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TITLE: Preparation of Chemicals and Bulk Drug Substances for the U.S. Army Drug Development Program

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CONTRACTING ORGANIZATION: Ash Stevens Inc.
Detroit, MI 48202-3398

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The purpose of the contract is to provide a variety of high purity chemicals and bulk drug substances for the U.S. Army Medical R & D Command. During the 12 months, eighteen assignments were completed. Compounds prepared and submitted include the antimalarial WR 238605, one metabolite of WR 238605, four potential metabolites of WR 242511, four pyridinecarbamates, one substituted benzenesulfonamide, two benzenesulfonyl chlorides, and a 3-deazapurine. In addition, racemic desbutylhalofantrine and WR 242511 were resolved to provide samples of the optically active enantiomers.

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FOREWORD

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P. Blumbergs 12/31/96

PI - Signature Date

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1. INTRODUCTION

The work described herein was performed under Contract No. DAMD17-93-C-3002 for the Division of Experimental Therapeutics, Walter Reed Army Institute of Research. The report covers the period 1 December 1995 to 30 November 1996. Dr. P. Blumbergs served as Principal Investigator and Dr. C.L. Stevens as Technical Advisor.

The purpose of the contract is to maintain and operate a synthesis laboratory to provide a wide variety of high purity chemicals and bulk drug substances required by various USAMRDC drug development programs (potential prophylactic and therapeutic drugs against parasitic and infectious diseases, and chemical and biological agents). Assignments of materials to be prepared were received from, and all of the synthesized products were delivered to the Department of Medicinal Chemistry, Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR).

Compounds prepared and submitted are listed below and form the subject matter of this report. These will be discussed in Section 2. Work in progress and assigned compounds will be presented in Section 3, experimental details in Section 4 and references cited in Section 5.

Work for the year ending November 30, 1995 was reported in the previous Annual Report (1).

The following 18 assignments were completed during the past twelve months.

1) (R)-(-)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline hemisuccinate (WR 280510)

   The title compound, 5 g, was shipped to WRAIR on December 19, 1995, Code No. CT-6-284, Bottle No. BN65139.

2) (S)-(+)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline hemisuccinate (WR 280511)

   The title compound, 5 g, was shipped to WRAIR on December 19, 1995, code No. CT-6-287, Bottle No. BN65148.

3) 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate (WR 238605)

A 1.06 kg lot of the title compound was shipped to WRAIR on January 17, 1996, Code No. KB-02-201, Bottle No. BN65479.

4) 3-Dimethylaminocarbonyloxypyridine (WR 256235)

A 5 g sample of the title compound was shipped to WRAIR on February 12, 1996, Code No. DJD-14-181, Bottle No. BN67571.

5) 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-5-hydroxy-4-methylquinoline dihydrochloride (WR 280528)

The title compound, 4 g, was shipped to WRAIR on February 21, 1996, Code No. CT-7-18, Bottle No. BN67759.

6) 3-Methylaminocarbonyloxypyridine (WR 178197)

The title compound, 3.5 g, was shipped to WRAIR on February 21, 1996, Code No. DJD-14-189, Bottle No. BN67740.

7) 1-Methyl-3-methylaminocarbonyloxypyridine iodide (WR 280593)

The title compound, 2 g, was shipped to WRAIR on March 27, 1996, Code No. DJD-14-199, Bottle No. BN69235.

8) 3-Dimethylaminocarbonyloxypyridine 1-oxide (WR 280594)

The title compound, 6 g, was shipped to WRAIR on March 27, 1996, Code No. DJD-14-210, Bottle No. BN69244.

9) 8-[(4-Amino-1-methylbutyl)amino]-5-hydroxy-6-methoxy-4-methylquinoline dihydrobromide (WR 280612)

The title compound, 8 g, was shipped to WRAIR on April 17, 1996, Code No. CT-7-52, Bottle No. BN70176.

10) N,N-Dimethyl-2-fluoro-5-(trifluoromethyl)benzene-sulfonamide (WR 280649)

A 1 g sample of the title compound was shipped to WRAIR on June 3, 1996, Code No. CT-7-87, Bottle No. BN71084.

11) 2-Fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (WR 280675)

The title compound, 40 g, was shipped to WRAIR on June 11, 1996, Code No. CT-7-95, Bottle No. BN71735.

12) 8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-hydroxy-4-methylquinoline dihydrochloride, half-hydrate (WR 280682)

A 7 g sample of the title compound was shipped to WRAIR on June 19, 1996, Code No. DJD-14-258, Bottle No. BN72116.

13) (+)-α-[2-(Butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol hydrochloride (WR 280823)

The title compound, 1.2 g, was shipped to WRAIR on September 9, 1996, Code No. CT-7-133, Bottle No. BN78896.

14) (-)-α-[2-(Butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol hydrochloride (WR 280691)

The title compound, 1.2 g, was shipped to WRAIR on September 9, 1996, Code No. CT-7-136, Bottle No. BN78903.

15) 1,5-Dihydro-4H-imidazo[4,5-c]pyridin-4-one (WR 280824)

A 0.5 g sample of the title compound was shipped to WRAIR on September 9, 1996, Code No. DJD-14-290, Bottle No. BN78912.

16) 8-[(3-Carboxy-1-methylpropyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (WR 280829)

The title compound, 2 g, was shipped to WRAIR on September 24, 1996, Code No. CT-7-143, Bottle No. BN79811.

17) 2-Chloro-5-(trifluoromethyl)benzenesulfonyl chloride (WR 280846)

The title compound, 50 g, was shipped to WRAIR on October 9, 1996, Code No. CT-7-154, Bottle No. BN80547.

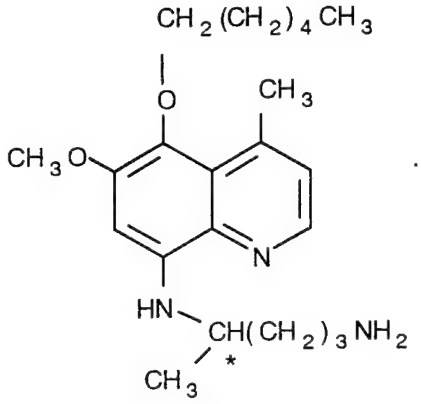
18) 8-[(4-Amino-1-methylbutyl)amino]-5,6-dihydroxy-4-methylquinoline hydrobromide, hydrate (WR 280870)

The title compound, 1 g, was shipped to WRAIR on November 12, 1996, Code No. CT-7-166, Bottle No. BN82390.

2. RESULTS AND DISCUSSION

Assignments completed during the past twelve months are discussed below.

2.1 (R)- And (S)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline hemisuccinate



* R and S enantiomers

The request was to prepare 5-10 g of each enantiomer of WR 242511. To the best of our knowledge, synthesis of the optically pure enantiomers has not been reported in the chemical literature. Accordingly, a synthesis route had to be developed in the current study. Of the two general approaches, asymmetric synthesis and resolution of the racemic material, the former was deemed less desirable based on our previous experience with WR 238605. As reported earlier (1), attempts to prepare optically pure WR 238605 via asymmetric synthesis gave unsatisfactory results. Considerable racemization took place in a key coupling reaction. For this reason, our main emphasis was placed on the resolution of racemic WR 242511 and only a limited effort was expended on the asymmetric synthesis approach. The results of this work are described in the following three subsections.

2.1.1 Resolution of WR 242511

The successful resolution of the analogous 8-aminoquinoline WR 238605 via a dibenzoyltartrate salt was described in a previous report (1). Accordingly, we expected that dibenzoyltartaric acid would be the resolving agent of choice for WR 242511.

Treatment of the racemic free base with dibenzoyl-L-tartaric acid gave a crystalline salt which could be readily recrystallized from ethanol. Product recovery was poor, however, and multiple crystallizations were required to effect resolution. The partly enriched crystallization mother liquors were converted to the dibenzoyl-D-tartaric acid salt which similarly required multiple recrystallizations. Part way through the resolution process, it was established from elemental analysis results that partial loss of benzoyltartaric acid had taken place during the repeated recrystallizations, and the crystalline resolved product was a hemi-salt. In light of these results, a portion of the partially resolved WR 242511 was converted directly to the half-salts of dibenzoyl-D- and L-tartaric acids. Sadly, this change failed to improve the resolution process. Multiple recrystallizations were still required to effect resolution. Different recrystallization solvents, namely tetrahydrofuran, dioxane, methanol, isopropanol, acetone, ethyl acetate, and toluene were evaluated but gave either poor recovery or poor selectivity. Several different resolving agents were evaluated also. These included (+)-2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA), (+)-4'-nitrotartranilic acid, dibenzoyltartaric acid mono(dimethylamide), and L-tartaric acid. All of these failed to give good crystalline salts.

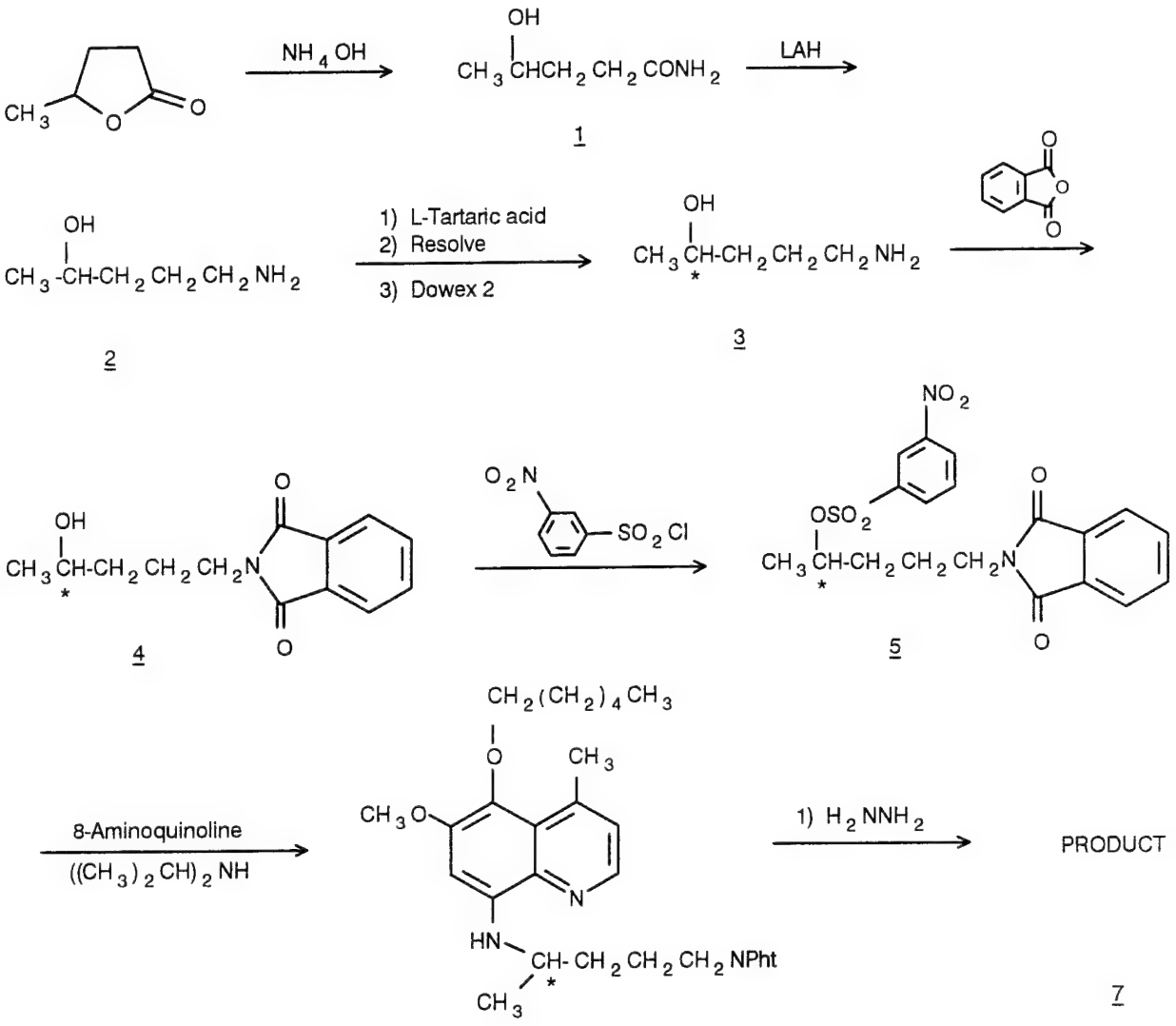
Another factor complicating the resolution was the apparent poor stability of WR 242511. Thus, during the fractional crystallization process, the crystallization mother liquors turned progressively darker as a result of decomposition caused by excess acid and/or air-oxidation. Analysis by thin-layer chromatography (TLC) showed the formation of extraneous sideproducts. Nevertheless, even though the process was tedious and inefficient, it did lead to pure S-(+) and R-(-) enantiomers of WR 242511. Both enantiomers were converted to, and characterized as the crystalline hemisuccinate salts.

2.1.2 Asymmetric synthesis of S-(+)-WR 242511

As stated above, only minimal effort was expended on this approach. The synthesis route is shown in Chart No. 1 and is the same as that used in the attempted stereospecific synthesis of WR 238605. Intermediate 5 of R(-)-configuration was available from previous work (1). A sample of this material was coupled with the properly substituted 8-aminoquinoline to give, after column chromatography, pure phthalimide product 6, $[\alpha]_D$ + 8.7°. Treatment of compound 6 with hydrazine gave WR 242511 free base with $[\alpha]_D$ + 8.3°. Inasmuch as the optically pure product should have a rotation of 30° (see below), it is clear that considerable racemization took place during the coupling reaction. Any optical activity present is expected to result from inversion at

CHART NO. 1

(S)-8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY)-6-METHOXY-4-METHYLQUINOLINE



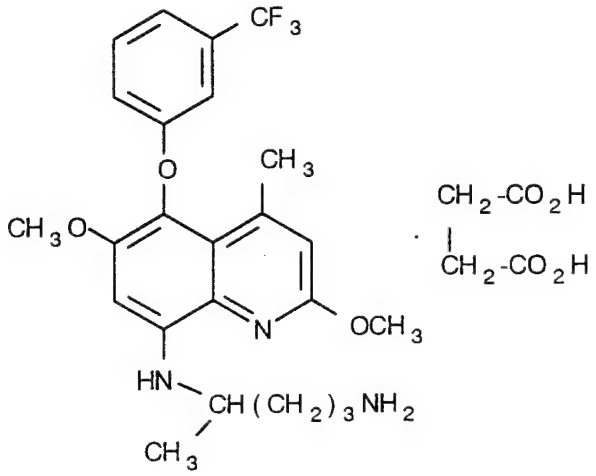
the optical center and, since intermediate 5 had the R-configuration, the dextrorotatory product 7 has the S-configuration. Proper modifications in the synthesis route could, quite possibly, lead to a product with improved optical purity. This was not pursued in the current study, however.

2.1.3 Optical purity analysis of resolved WR 242511

Based on the optical rotation of resolved WR 238605 (1), we expected the pure enantiomers of the structurally related WR 242511 to have a rotation of ca. 30°. We considered it desirable, however, to establish a method by which the optical purity of the enantiomers could be verified. As a first approach, the method described by Mosher (2) and used by us to determine the optical purity of resolved WR 238605 (1), was evaluated. This involved the derivatization of the chiral compound with a chiral reagent to give a mixture of diastereomers which was then analyzed by nuclear magnetic resonance (NMR) spectroscopy.

Thus, racemic WR 242511 was treated with S-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride to give a monoamide derivative. The proton NMR spectrum of the product showed separate signals for the quinoline 6-methoxy groups, one for each enantiomer of WR 242511. However, the peaks were fairly close to each other such that integration of the signals from an optically impure product would give inaccurate results due to signal overlap. Based on the literature report that fluorine NMR gives better results (2), a sample of partially resolved WR 242511, $[\alpha]_D$ + 4.67°, was converted to the same monoamide derivative and analyzed by ^{19}F NMR. The spectrum showed two peaks in a ratio of 1.37:1. A simple calculation revealed that within experimental error, the pure enantiomers should have a rotation of 30°. Finally, a sample of the resolved compound ($[\alpha]_D$ -29.5°) was derivatized and analyzed by ^{19}F NMR. The spectrum showed only one singlet. Although the method was not quantitated, we believe the optical purity of both enantiomers to be in excess of 95%.

2.2 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate (WR 238605)



Two lots of the title compound, 1.32 kg and 2.49 kg were prepared and delivered under earlier contracts (3,4). The current request was for 1 kg. The compound was prepared via the reaction sequence shown in Chart No. 2 which is the same as that used in the previous work. Minor modifications were made in some of the steps and these are discussed below. Synthesis of the 5-hydroxyquinoline starting material was described in a prior report (5).

Turning to Chart No. 2, treatment of 5-hydroxy-6-methoxy-5-methyl-8-nitroquinoline with phosphorus oxychloride gave the 5-chloro compound 1 which, after purification, was treated with m-hydroxybenzotrifluoride and potassium hydroxide to give product 2. The nitro group in compound 2 was reduced with iron-acetic acid and the product amine 3 was converted to the phthalimide 4 by reaction with phthalic anhydride in toluene-xylene solvent mixture.

Oxidation of compound 4 to the N-oxide 5 proceeded satisfactorily and gave a good yield of crude product. An unexpected problem was encountered in the purification step, however. Recrystallization of the crude material from ethanol generated a new impurity. Further recrystallization of the product from a toluene-ethanol mixture gave pure intermediate 5 but the yield was lower than in previous preparations. The new "impurity" was isolated in pure form and, based on NMR and elemental analysis results, was the 8-phthalamide ethyl ester.

CHART NO. 2

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-2,6-DIMETHOXY-5-(3-TRIFLUOROMETHYLPHENOXY)QUINOLINE SUCCINATE (WR 238605)

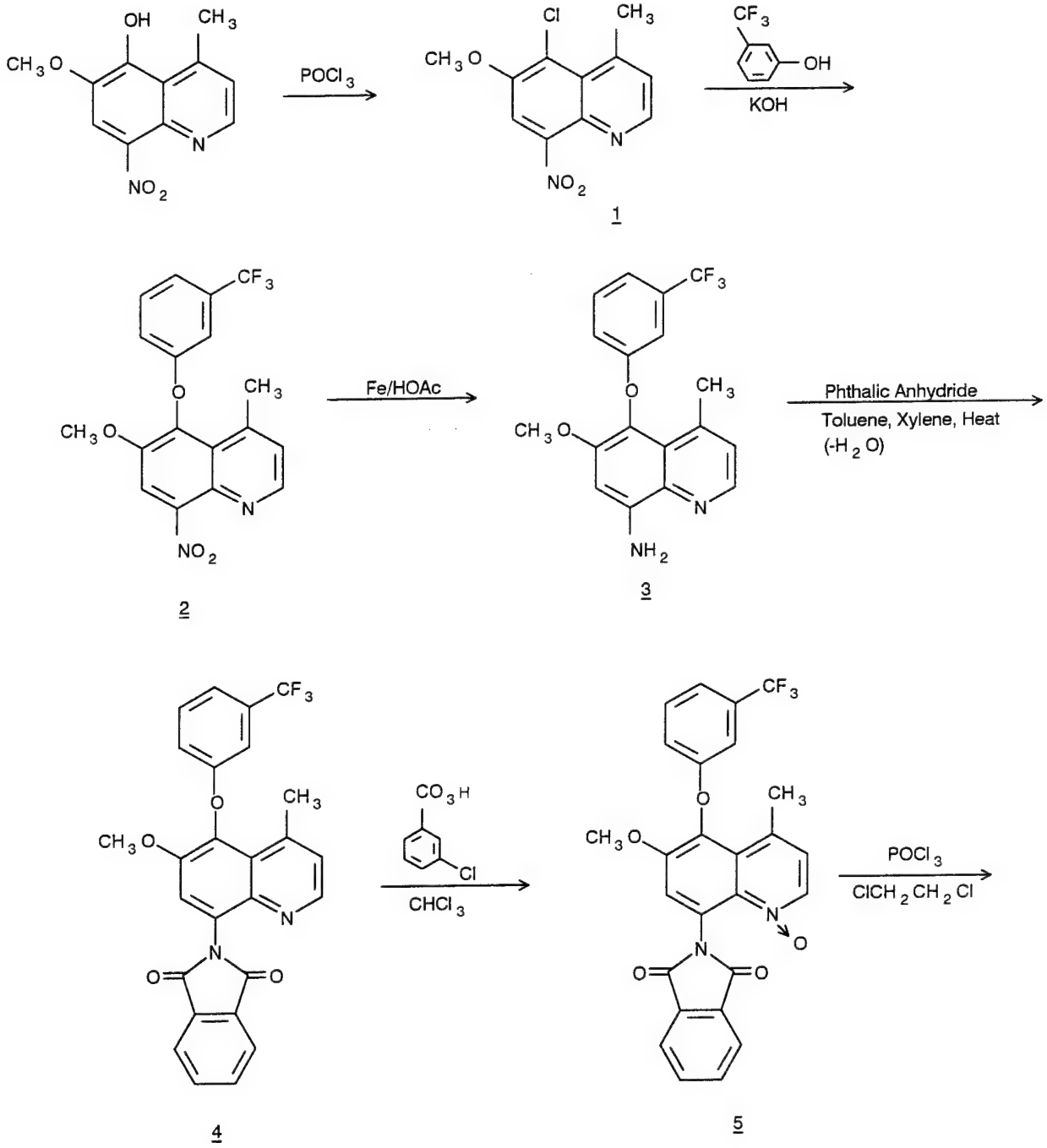
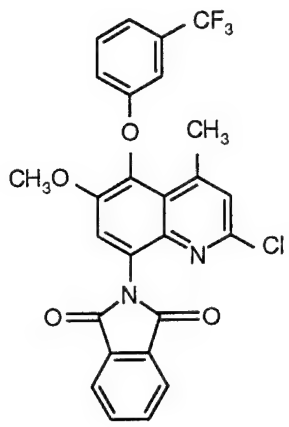


CHART NO. 2 (Continued)



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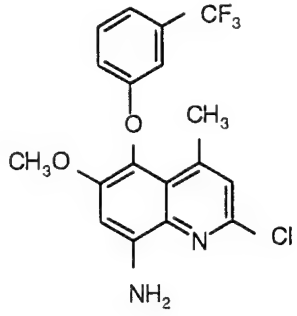

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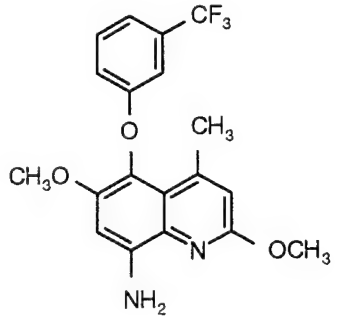

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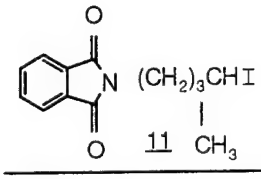

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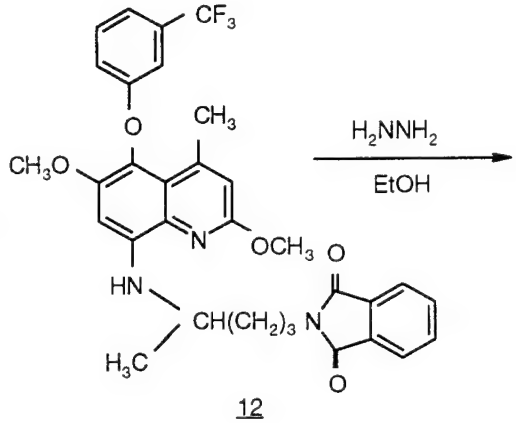
(See below for preparation of 11)



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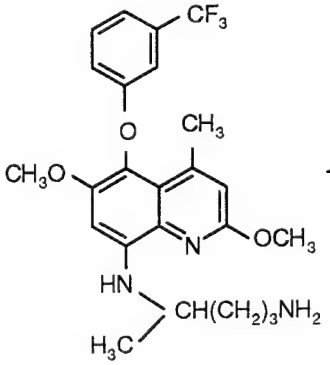
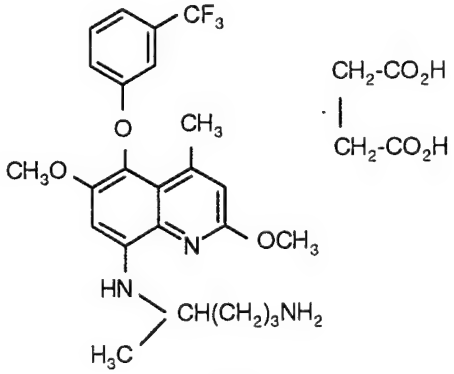


13

(free base, thick oil)

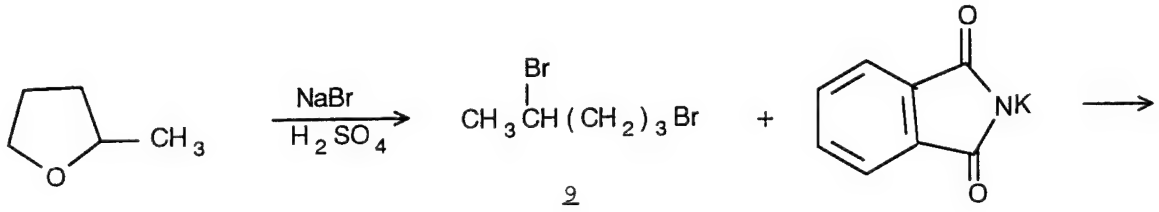


14

WR 238605·Succinate

CHART NO. 2 (Continued)

Preparation of 4-Iodopentylphthalimide (11)



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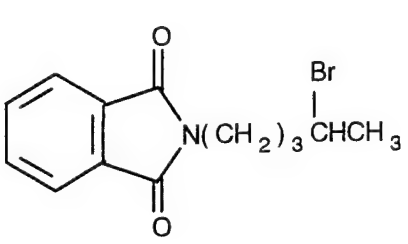

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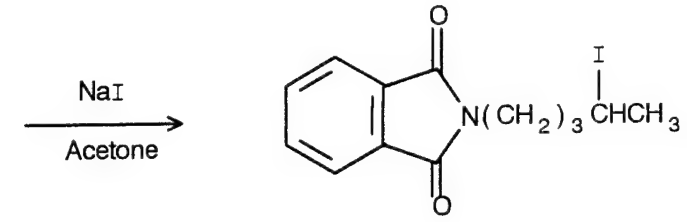


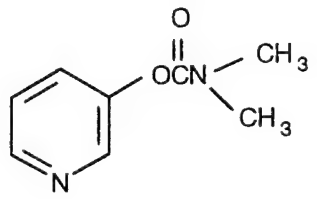
11

Treatment of this impurity with phosphorus oxychloride converted it to 2-chloroquinoline 6 and therefore it would not have adversely affected the quality of the final product. Nevertheless, only the purified intermediate 5 was used in the current preparation.

For the conversion of compound 5 to 2-chloroquinoline 6, chloroform was used previously as the reaction solvent. In view of the high disposal costs of waste chloroform, other solvents (methylene chloride and ethylene dichloride) were evaluated as possible substitutes. Small scale trial reactions proceeded equally well in all three solvents. Accordingly, chloroform was replaced with ethylene dichloride in this step.

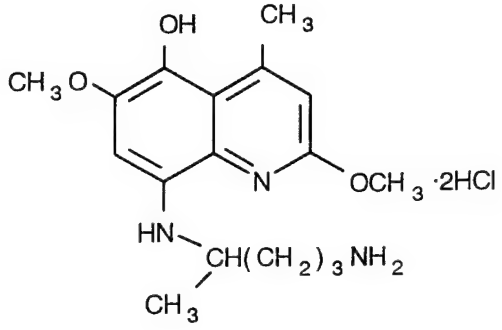
The rest of the reaction sequence remained unchanged from that used previously. Thus, intermediate 6 was deblocked with hydrazine to afford the 8-amino-2-chloroquinoline 7 which was treated with methoxide to give the 8-amino-2-methoxyquinoline 8. The sidechain reagent 11 was prepared by a standard three-step sequence, then coupled with quinoline 8 to give the protected product 12. Compound 12 was deprotected with hydrazine and the product, WR 238605 free base (13) was treated with succinic acid to give, after two recrystallizations, pure WR 238605 succinate salt.

2.3 3-Dimethylaminocarbonyloxypyridine (WR 256235)



The title compound was prepared by a general literature procedure (6,7) which involved the reaction of 3-hydroxypyridine with dimethylcarbamyl chloride in the presence of triethylamine. Removal of triethylamine hydrochloride followed by fractional distillation gave pure title compound in the form of a clear colorless oil.

2.4 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-5-hydroxy-4-methylquinoline dihydrochloride (WR 280528)



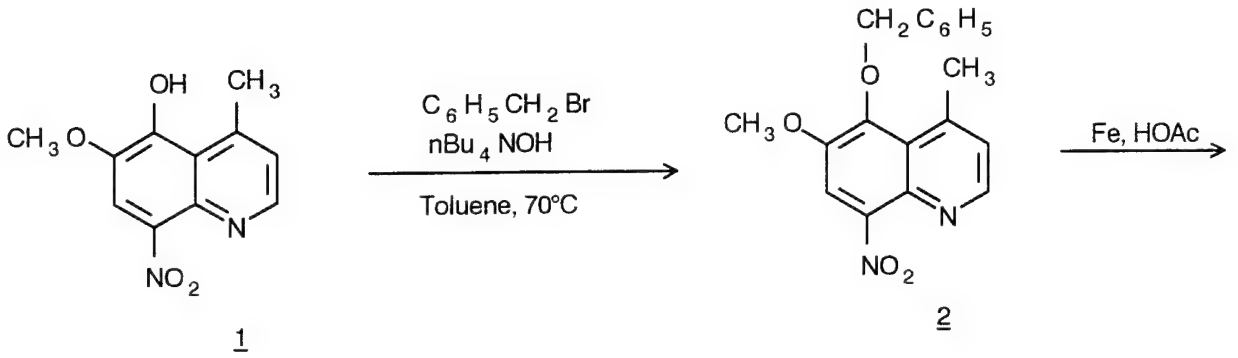
To the best of our knowledge, synthesis of the title compound, a potential metabolite of WR 238605, has not been reported in the open literature. The synthesis route used successfully in the current work is shown in Chart No. 3. This same route, through intermediate 8, was used by us previously to prepare another potential metabolite of WR 238605 (8).

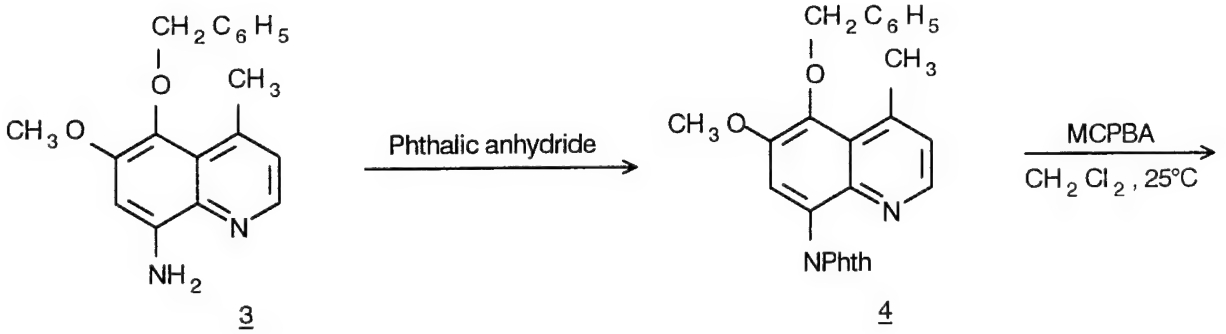
By this route, the 5-hydroxy-8-nitroquinoline 1 was alkylated with benzyl bromide to give the 5-benzyloxyquinoline 2. The 8-nitro group of quinoline 2 was reduced with iron-acetic acid and the product, 8-aminoquinoline 3, was heated with phthalic anhydride in toluene as solvent to yield the 8-phthalimidoquinoline 4. Compound 4 was oxidized with m-chloroperbenzoic acid to the N-oxide 5, which was treated with phosphorus oxychloride to give 2-chloroquinoline 6. Next, the 8-phthalimide protection was removed with hydrazine and the resulting 2-chloro-8-aminoquinoline 7 was treated with sodium methoxide to introduce the 2-methoxy group. The product, quinoline 8, was coupled with 4-iodo-1-phthalimidopentane in the presence of potassium carbonate to give intermediate quinoline 9. Treatment of compound 9 with hydrazine cleaved the phthalimide to give quinoline 10. Unexpectedly, compound 10 free base proved to be quite air-sensitive. Considerable discoloration took place even though the reaction of 9 with hydrazine and the isolation of 10 was carried out under a nitrogen atmosphere. The dihydrochloride salt was sufficiently stable to permit recrystallization but product yield was only fair.

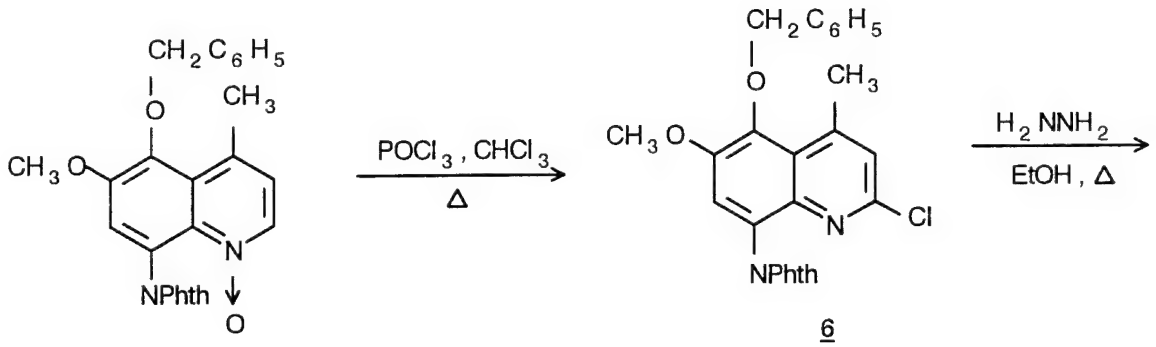
CHART NO. 3

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-HYDROXY-

2,6-DIMETHOXY-4-METHYLQUINOLINE (WR 280528)







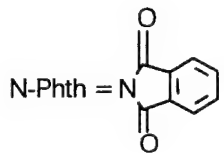
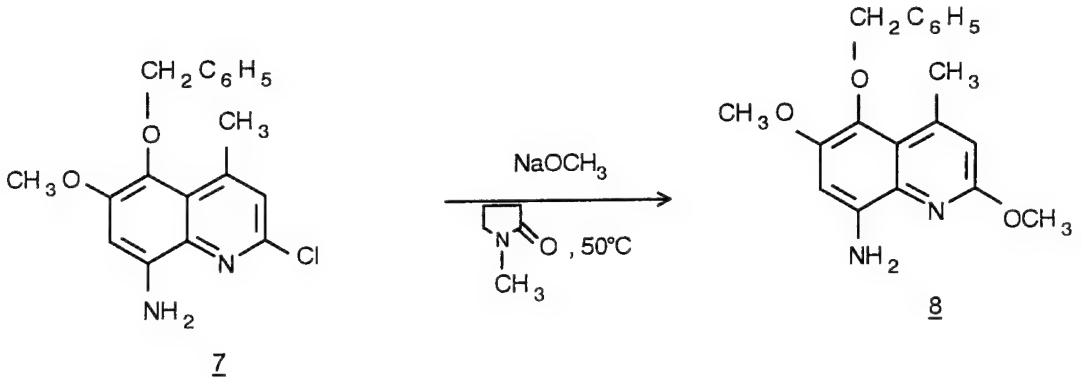
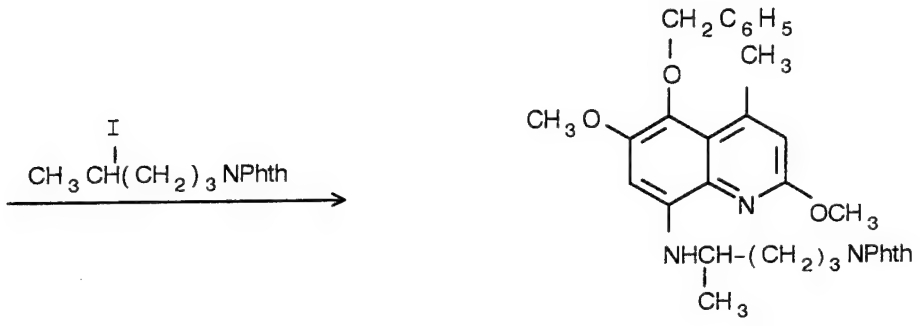


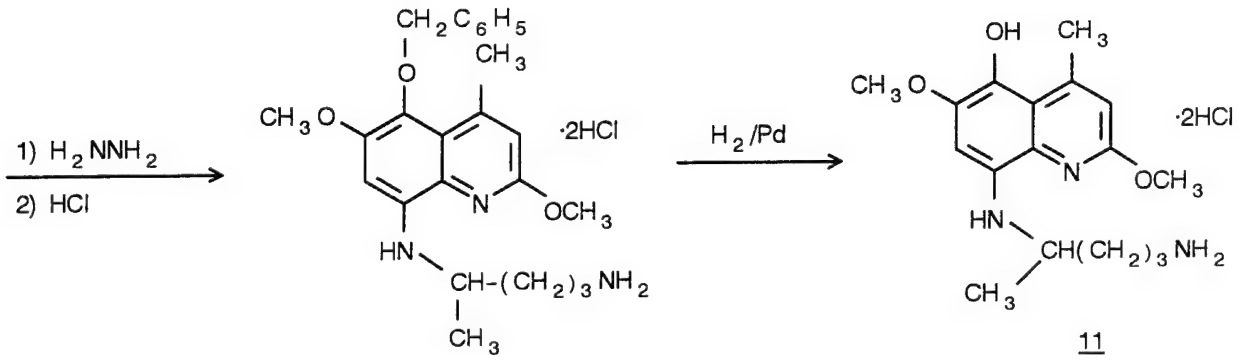
CHART NO. 3 (Continued)



7 8



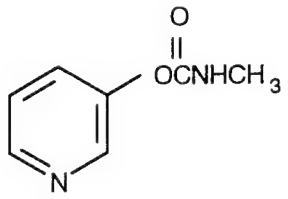
9



10 11

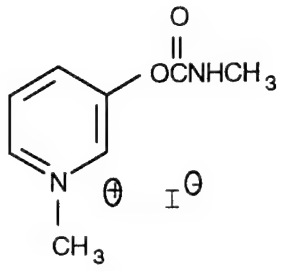
The last step of the reaction sequence calls for cleavage of the 5-benzyloxy group. This was accomplished by hydrogenation of precursor 10 over palladium black catalyst. Compound 11 dihydrochloride salt was isolated readily in a crystalline form and appeared to be stable as the crystalline solid when stored under an inert atmosphere. Analysis of the product by TLC on silica gel plates proved to be highly unsatisfactory. The compound decomposed when spotted on the plate as evidenced by rapid discoloration. Better results were obtained using cellulose plates. Although the product tended to streak somewhat, decomposition appeared to be minimal. In solution, the compound decomposed when exposed to atmospheric oxygen relatively slowly under acidic conditions but quite rapidly (within minutes) under basic conditions. Accordingly, we recommend the use of degassed solvents and inert atmosphere when handling solutions of compound 11.

2.5 3-Methylaminocarbonyloxypyridine (WR 178197)



Synthesis of the title compound by the reaction of 3-hydroxypyridine with methyl isocyanate has been reported in the literature (6). The same approach was used in the current work. Thus, 3-hydroxypyridine was treated with methyl isocyanate at room temperature to give, after removal of excess isocyanate, crude product. Purification of the crude material by distillation failed. The compound underwent partial decomposition at the distillation temperature (90-95°C) with the regeneration of 3-hydroxypyridine. The reaction was repeated using recrystallized 3-hydroxypyridine to give the product in the form of a tan oil. The oil crystallized when refrigerated but the solid melted at room temperature. This product had acceptable elemental analysis and the NMR spectrum was consistent with the structure. Accordingly, no further purification was carried out.

2.6 <u>1-Methyl-3-methylaminocarbonyloxypyridine iodide (WR 280593)</u>



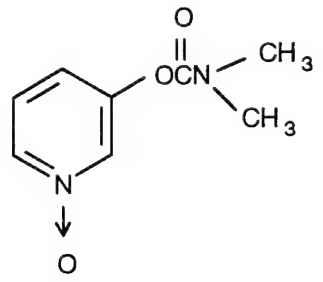
The title compound was prepared by the quaternarization of 3-methylaminocarbonyloxypyridine.

In the first attempt, treatment of the 3-pyridinol carbamate of section 2.5 with methyl iodide in tetrahydrofuran solvent gave a light yellow crystalline product. Attempted recrystallization of the compound led to partial decomposition due to excessive heating during recrystallization. The reaction was repeated and a portion of the solid was recrystallized using less heat to give a sharp-melting crystalline product. The compound had acceptable elemental analysis in carbon, hydrogen and nitrogen and the NMR spectrum was consistent with the structure.

Purity analysis by high-pressure liquid chromatography (HPLC) gave unsatisfactory results. Due to the highly polar nature of the compound, we used a reverse phase column and water-acetonitrile as the eluant. Nevertheless, the compound eluted as a broad band. In addition, the compound underwent fairly rapid hydrolysis in this solvent system. Thus, when a water-acetonitrile (85:15) solution of the carbamate was stored at room temperature for 1-2 hours, the only product detected by HPLC was 1-methyl-3-hydroxypyridine.

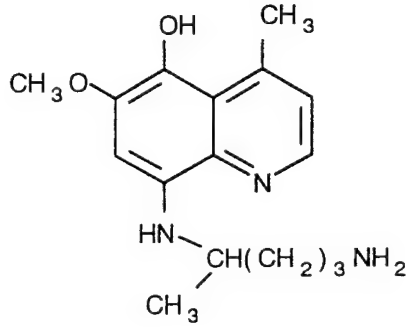
Since the proton NMR spectrum of the recrystallized title compound was wholly consistent with the structure and showed the absence of extraneous signals attributable to impurities, we felt the product to be of acceptable quality.

2.7 3-Dimethylaminocarbonyloxypyridine 1-oxide (WR 280594)



The title compound was prepared by the oxidation of 3-dimethylaminocarbonyloxypyridine. Thus, the carbamate was treated with 3-chloroperoxybenzoic acid in methylene chloride to give the crude N-oxide. Purification by column chromatography followed by recrystallization gave pure title N-oxide.

2.8 8-[(4-Amino-1-methylbutyl)amino]-5-hydroxy-6-methoxy-4-methylquinoline (WR 280612)



The title compound is a potential metabolite of WR 242511. To the best of our knowledge, synthesis of this structure has not been reported in the open literature. The compound was prepared by the synthesis route shown in Chart No. 4.

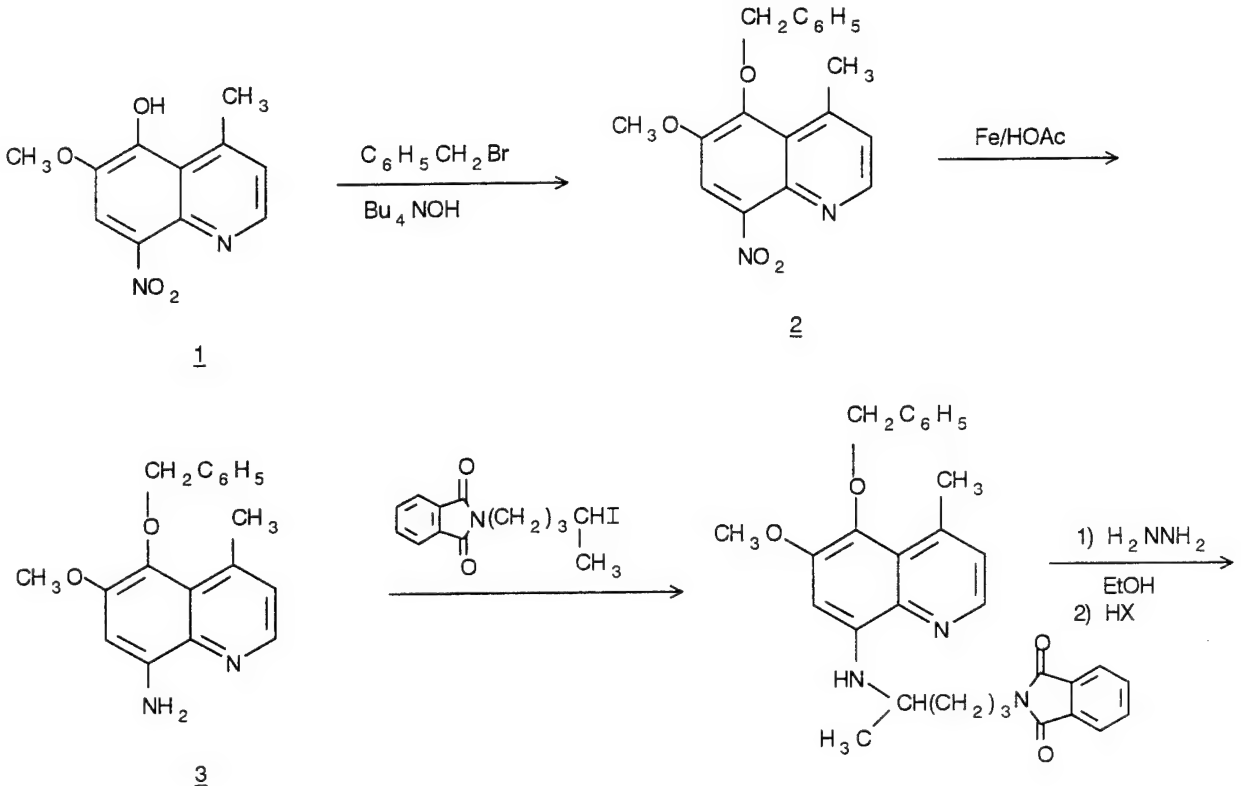
Synthesis of the starting 5-hydroxyquinoline 1 was described in a previous report (5), and the preparation of compounds 2 and 3 is described in section 2.4 above. In the next step of the sequence, quinoline 3 was coupled with 4-iodopentyl-phthalimide in the presence of anhydrous potassium carbonate using N-methyl-2-pyrrolidinone as solvent. Chromatography of the product mixture led to the isolation of the alkylated quinoline 4, a red, thick oil. Attempts to obtain compound 4 in the form

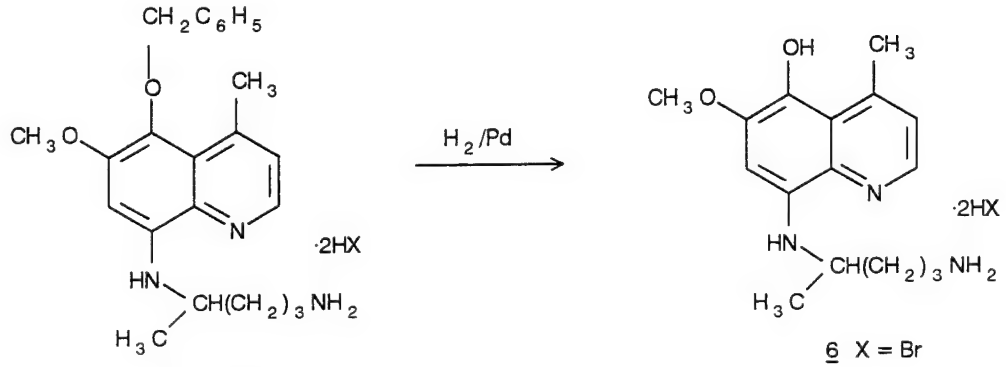
of a crystalline solid failed. Accordingly, the compound was deprotected with hydrazine and the product was purified by chromatography, then converted to a dihydrochloride salt to give a dark red, crystalline solid with acceptable elemental analysis for structure 5a.

In the last step, cleavage of the 5-O-benzyl group of compound 5a by hydrogenolysis appeared to proceed readily but the product could not be induced to crystallize. Removal of the solvent gave a purple foam. Alternatively, the product could be precipitated from solution in the form of an amorphous solid but the NMR spectrum showed that this material was contaminated with solvent and other extraneous impurities. Attempted conversion of quinoline 5 to a sulfate salt gave a black tar. Compound 5 did form crystalline salts with phosphoric, citric, and succinic acids. Hydrogenation of the phosphate salt gave a product which turned black upon attempted recrystallization. The citric acid salt gave similar results. Hydrogenation of the succinic acid salt gave a crystalline product 6 succinate but the compound, when in solution, was extremely air-sensitive and it was not possible to avoid partial decomposition during crystallization/ recrystallization. As a last attempt, the hydrobromic acid salt was evaluated. Compound 5 did form a crystalline dihydrobromide salt and hydrogenation of this material gave crystalline compound 6 dihydrobromide salt. The dihydrobromide was more stable than the succinic acid salt and could be readily recrystallized. The recrystallized product had acceptable elemental analysis and the NMR spectrum was consistent with the structure. In view of these results, the main lot of compound 5a was converted to the dihydrobromide 5b and hydrogenated to give, after recrystallization, pure title compound 6 dihydrobromide salt.

CHART NO. 4

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-HYDROXY-6-METHOXY-4-METHYLQUINOLINE (WR 280612)

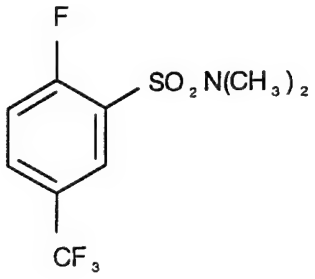




5a X = Cl
5b X = Br

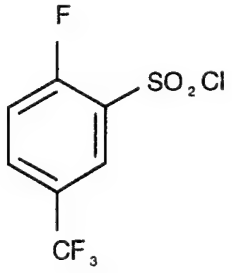
6 X = Br

2.9 N,N-Dimethyl-2-fluoro-5-(trifluoromethyl)benzene-sulfonamide (WR 280649)



The title compound was prepared by the reaction of 2-fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (prepared as described in section 2.10 below) with dimethylamine. The product had acceptable elemental analysis and the ^{1}H NMR and infrared (IR) spectra were consistent with the structure.

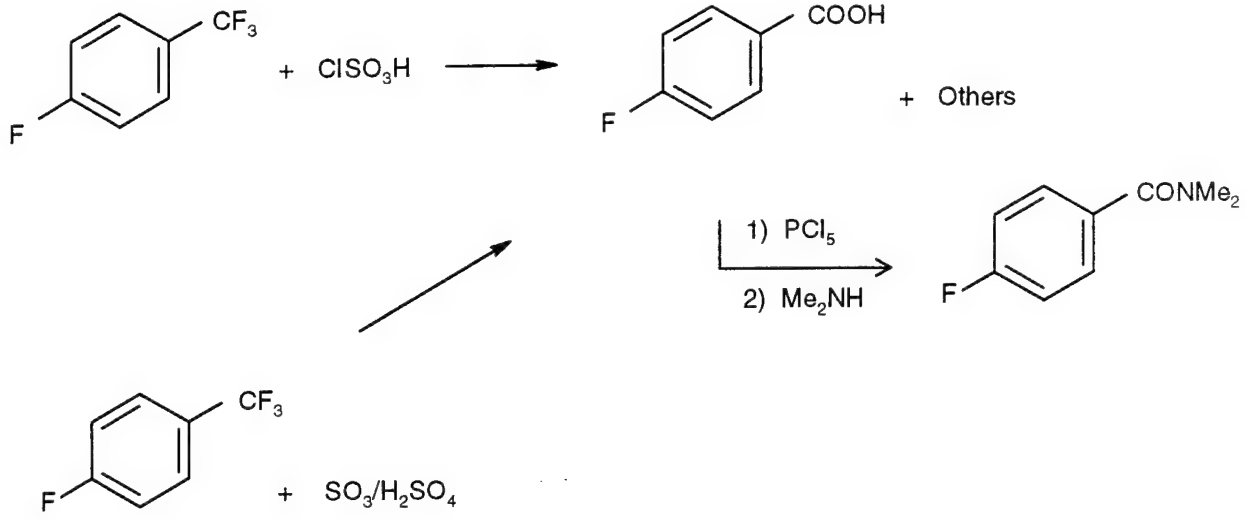
2.10 2-Fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (WR 280675)

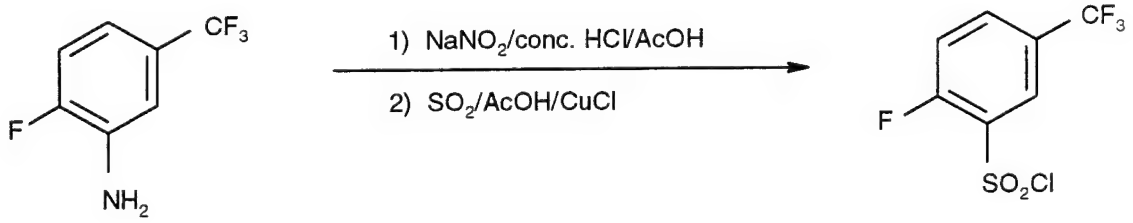


Preparation of the title compound was investigated by the routes shown in Chart No. 5. By the first approach, 4-fluorobenzotrifluoride was treated with excess chlorosulfonic acid under standard chlorosulfonation conditions. Workup of the reaction mixture gave two major products. One of these was an oil which was unreactive toward dimethylamine and showed two equal intensity signals for aromatic protons in the NMR spectrum. This clearly is not consistent with the expected product 1. The other reaction product was a crystalline, acidic solid, mp 183-185°C. This material was not characterized any further but was treated directly with phosphorus pentachloride followed by dimethylamine to give a new crystalline solid, mp 65.5-67.5°C, identified (NMR and elemental analysis) as N,N-dimethyl-4-fluorobenzamide. We note that literature reports mp 186°C for 4-fluorobenzoic acid (9) and mp 64°C for the amide (10).

CHART NO. 5

N,N-DIMETHYL-2-FLUORO-5-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE (WR 280846)

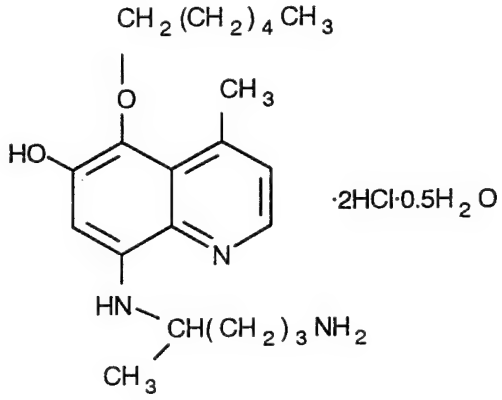




By the second approach, the benzotrifluoride was treated with 20% fuming sulfuric acid. This reaction gave the benzoic acid as a major product along with several minor reaction products.

In view of these results, an alternative, relatively standard route to arylsulfonyl chlorides was investigated (11). By this route, 2-fluoro-5-(trifluoromethyl)aniline was diazotized and the diazonium salt (in situ) was treated with a solution of sulfur dioxide in acetic acid containing cuprous chloride to give the title sulfonyl chloride. The crude product was passed through a silica gel column to remove a minor impurity and the purified product was distilled to give pure sulfonyl chloride in the form of a clear yellow oil which solidified in the freezer.

2.11 8[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-hydroxy-4-methylquinoline dihydrochloride, half-hydrate (WR 280682)



The title compound is a potential metabolite of WR 242511. To the best of our knowledge, it represents a new chemical structure not reported in the open literature. Synthesis of the compound was accomplished successfully by the route shown in Chart No. 6.

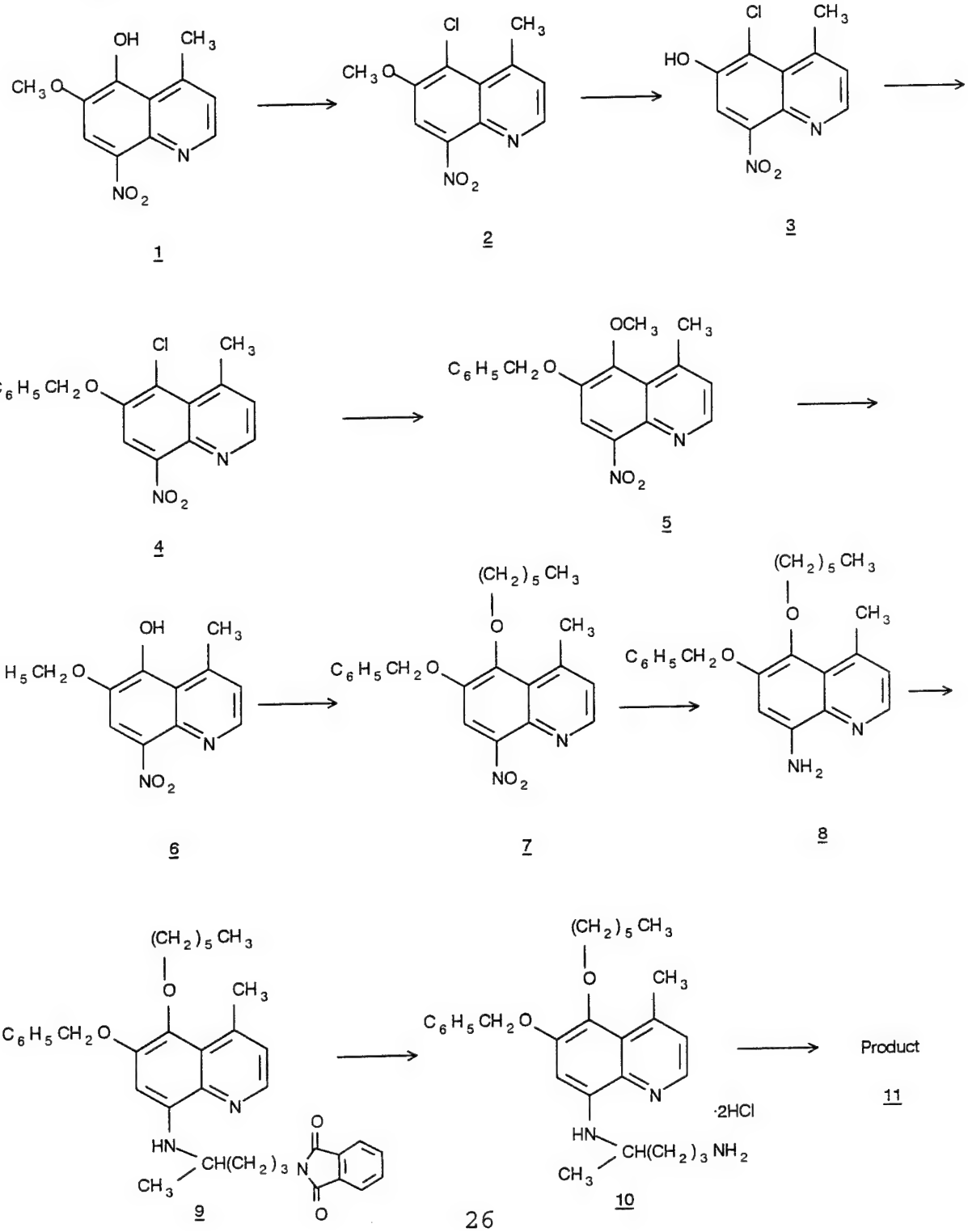
By this route, 5-hydroxyquinoline 1 was treated with phosphorous oxychloride to give 5-chloroquinoline 2. Attempts to cleave the 6-methoxy group of compound 2 with hydrobromic acid, trimethylsilyl iodide, boron tribromide, pyridine hydrochloride or methionine/methanesulfonic acid, failed. In all cases, only the formation of black decomposition products was observed. The methyl ether was cleaved readily, however, with anhydrous aluminum chloride to give the 6-hydroxyquinoline 3, which was alkylated with benzyl bromide to yield the 6-benzyloxyquinoline 4. Treatment of compound 4 with sodium hexyloxide did not yield

the desired 5-hexyloxyquinoline 7; only decomposition of 4 was observed. This is consistent with the literature which states that in the case of 5-chloroquinoline 2, the displacement reaction does not work with alcohols containing more than two carbon atoms (12). Displacement of the chloro group in compound 4 with potassium acetate in N-methylformamide failed also. No reaction was observed below 130°C and decomposition took place at higher temperatures. Displacement with sodium methoxide, although slow (72 h), proceeded well to give the 5-methoxyquinoline 5. Selective cleavage of the methyl ether was accomplished with refluxing, dilute hydrochloric acid-ethanol to give 5-hydroxyquinoline 6 in high yield. Compound 6 was treated with 1-bromohexane and tetrabutylammonium hydroxide to give the 8-nitro-5-hexyloxyquinoline 7, then reduced with iron-acetic acid to 8-aminoquinoline 8. The aminoalkyl sidechain was introduced in the standard way by the reaction of compound 8 with 4-iodopentylphthalimide and diisopropylethylamine to give the alkylated 8-aminoquinoline 9. Next, the phthaloyl blocking group was cleaved with hydrazine to yield quinoline 10 free base. This product was purified by chromatography, then converted to a crystalline dihydrochloride salt. In the last step, the 6-benzyl ether was cleaved by hydrogenolysis over palladium black catalyst to give the 6-hydroxyquinoline 11. The crude product was recrystallized twice and dried to give pure title compound as a half-hydrate.

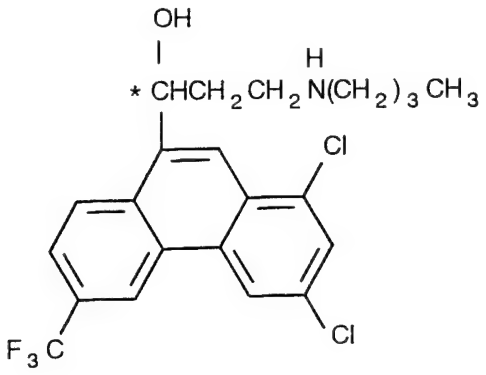
The crystalline dihydrochloride salt appeared to be relatively stable but the compound did undergo slow air-oxidation when in solution. The compound oxidized much faster under basic conditions when exposed to atmospheric oxygen.

CHART NO. 6

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY)-6-HYDROXY-4-METHYLQUINOLINE DIHYDROCHLORIDE (WR 280682)



2.12 Resolution of α-[2-(Butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol



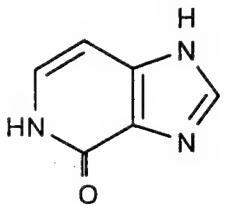
Resolution of the corresponding dibutylaminophenanthrenemethanol (halofantrine) by fractional crystallization of the d-camphoric acid salt has been reported in the literature to give the (+) and (-) enantiomers in 26 and 17% yield respectively (13). Our attempts to apply this procedure to the above monobutylamino compound, failed. Depending on the crystallization solvent employed, the salt either precipitated rapidly from solution without any apparent enantiomeric enrichment or failed to crystallize altogether. In view of this, other resolving agents were investigated.

Both, L-tartaric acid and dibenzoyl-L-tartaric acid gave crystalline salts in good yields. However, conversion of these salts back to the free base gave a product of negligible optical activity. Similarly, L-malic acid formed a crystalline salt which could be recrystallized but product recovery and enantiomeric enrichment were low. The di-p-toluoyl-L-tartaric acid (DTLTA) salt could not be induced to crystallize at room temperature from several solvent systems but did yield a broad melting crystalline product from acetone after extended refrigeration. In a repeat trial experiment, the DTLTA salt failed again to crystallize at room temperature (methanol-ethyl acetate) until the solution was seeded with the broad melting product obtained from acetone. Once initiated, crystallization was rapid to give a relatively sharp-melting product. Treatment

of the crystallization mother liquors with basic ion exchange resin led to the recovery of the title compound free base which showed considerable enantiomeric enrichment ($[\alpha]_D$ -20°). Accordingly, the process was repeated on a larger scale to yield, after three recrystallizations, pure DTLTA salt with a constant melting point. The mother liquors were treated with ion exchange resin and the recovered compound free base was converted to di-p-toluoyl-D-tartaric acid salt which required only two recrystallizations. Finally, both enantiomers were freed from the tartaric acid and converted to hydrochloride salts.

A sample of the (-)-enantiomer was analyzed by HPLC using a chiral column (courtesy WRAIR personnel) and showed high enantiomeric purity.

2.13 1,5-Dihydro-4H-imidazo[4,5-c]pyridin-4-one (WR 280824)



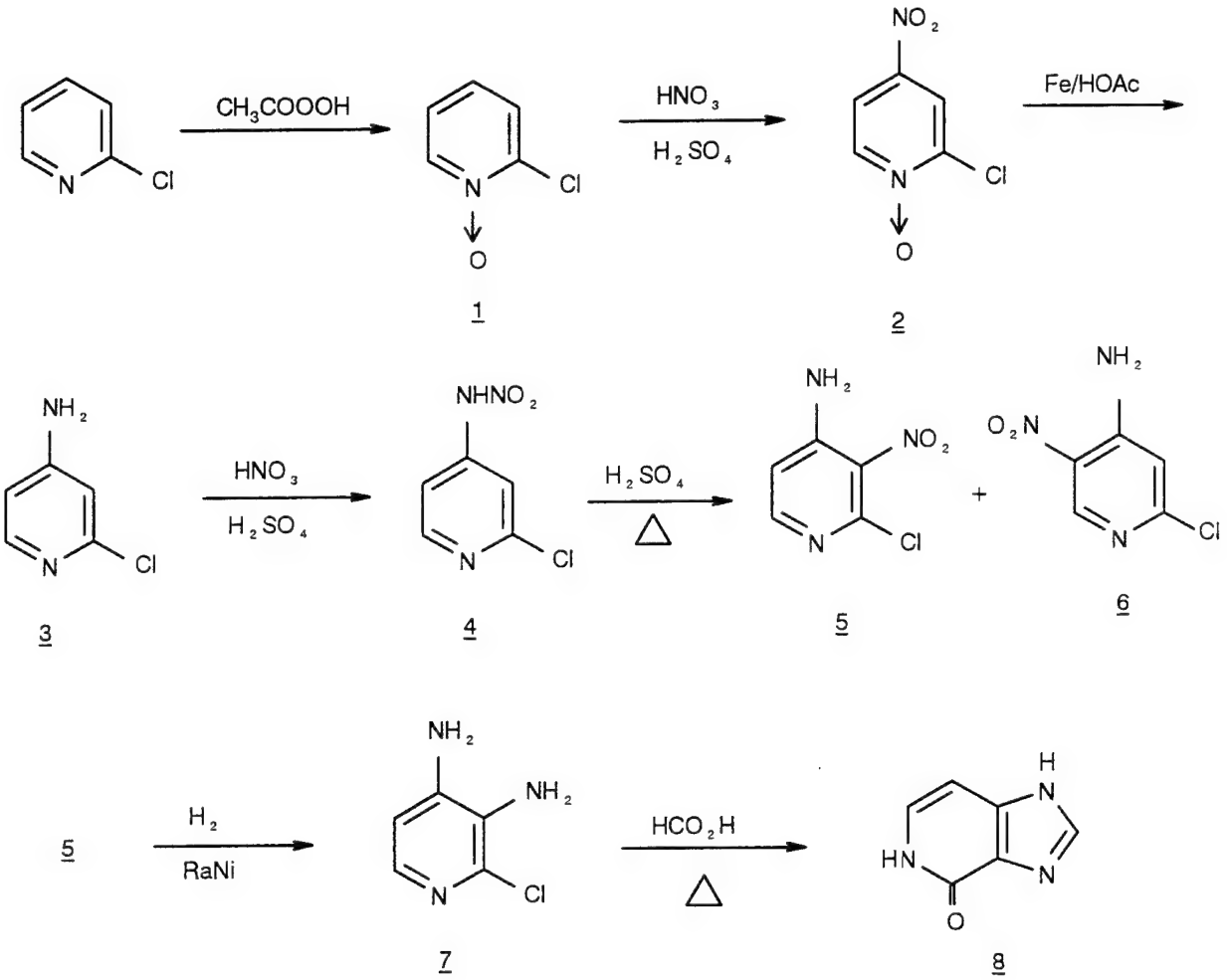
After a thorough literature search, the synthesis sequence shown in Chart No. 7 was chosen as the most straightforward route to the title compound.

Thus, 2-chloropyridine was oxidized with peracetic acid to give N-oxide 1. Nitration of compound 1 with fuming nitric acid in concentrated sulfuric acid gave the 4-nitropyridine 2. The reduction of compound 2 by hydrogenation over Raney nickel catalyst as reported in the literature (14) gave unsatisfactory results in our hands. Although compound 3 was formed, the yield was low and the product was contaminated with one major impurity. Better results were obtained using iron-acetic acid. No sideproducts were formed and compound 3 was isolated in high (91%) yield.

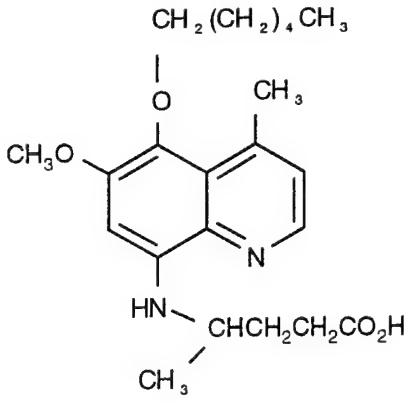
Nitration of compound 3 gave nitramine 4 which was rearranged in hot sulfuric acid to a mixture of nitropyridines 5 and 6. The isomers were separated by fractional crystallization and the pure 3-nitropyridine 5 was hydrogenated over Raney nickel catalyst to give crystalline diaminopyridine 7. In the last step, compound 7 was heated with formic acid at reflux (15) to give the title target compound 8.

CHART NO. 7

1,5-DIHYDRO-4H-IMIDAZOL[4,5-c]PYRIDIN-4-ONE (WR 280824)



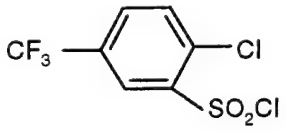
2.14 8-[(3-Carboxy-1-methylpropyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (WR 280829)



The title compound, a potential metabolite of WR 242511, was prepared by reductive alkylation of 8-amino-5-(1-hexyloxy)-6-methoxy-4-methylquinoline with levulinic acid and sodium cyanoborohydride. The crude reaction mixture was chromatographed over silica gel and the product oil was triturated with hexanes to give a light brown solid. This material was decolorized with charcoal and recrystallized from ether-petroleum ether to give pure title compound as bright yellow crystals.

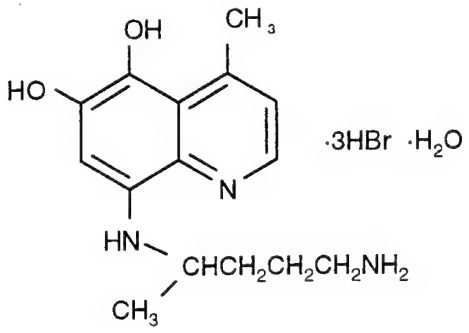
The compound was stable in the solid form and in ether solution. In chloroform solution, the compound formed a new product which most likely is the cyclic lactam.

2.15 2-Chloro-5-(trifluoromethyl)benzenesulfonyl chloride (WR 280846)



The title compound was prepared from 2-chloro-5-(trifluoromethyl)aniline. Thus, the aniline was diazotized with sodium nitrite/hydrochloric acid and the diazonium salt was treated with sulfur dioxide and cuprous chloride to give crude title sulfonyl chloride. The crude product was passed through a silica gel column to remove a minor impurity and the purified product was distilled to give pure sulfonyl chloride in the form of a clear yellow oil which solidified in the freezer.

2.16 8-[(4-Amino-1-methylbutyl)amino]-5,6-dihydroxy-4-methylquinoline hydrobromide, hydrate (WR 280870)

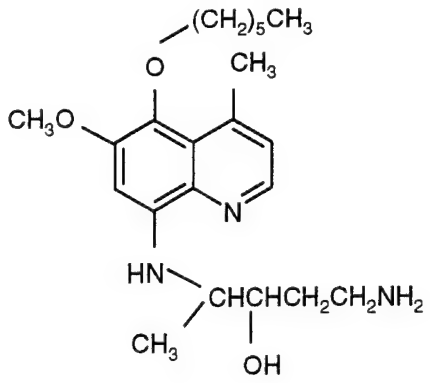


The title compound is another potential metabolite of WR 242511.

As a first approach to this target structure, a small retainer sample of the 5-hydroxy-6-methoxy analog was treated with 48% hydrobromic acid at reflux for 2 h. Concentration of the mixture to dryness followed by crystallization of the residue gave a beige solid. Based on ^{1}H NMR, this solid appeared to be the title compound, contaminated with about 10% of the 6-methoxyquinoline starting material. Inasmuch as we had only a small amount of the 6-methoxy compound on hand, other synthesis routes were evaluated. Hydrolysis of the 5-hexyloxy-6-benzyloxy substituted quinoline with hydrobromic acid proceeded more readily and gave better quality product. As a final approach, previously prepared 8-[(4-amino-1-methylbutyl)amino]-6-benzyloxy-5-(1-hexyloxy)-4-methylquinoline dihydrochloride (compound 10, section 2.11) was converted to the dihydrobromide salt and hydrogenated over palladium black to give the 6-hydroxyquinoline dihydrobromide which was treated directly with 48% hydrobromic acid to give the title compound hydrobromide salt. The product appears to form a trihydrobromide salt that partially dissociates during recrystallization and/or drying at reduced pressure. For purification, the crude product was recrystallized from a mixture of methanol-ethanol-petroleum ether containing some hydrobromic acid. Elemental analysis of the dried final product was consistent with a 2.9 hydrobromide hemihydrate and the ^{1}H NMR spectrum was in agreement with the structure.

3. WORK PROGRESS AND ASSIGNED COMPOUNDS

3.1 8-[(4-Amino-2-hydroxy-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline



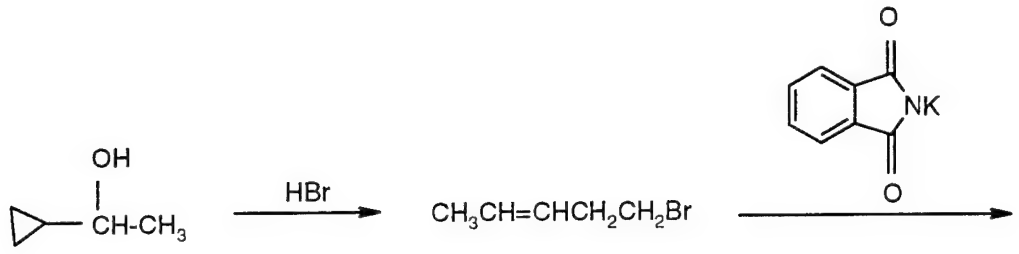
The title compound is a potential metabolite of WR 242511. Attempts to synthesize this compound by alkylation of the precursor 8-aminoquinoline 4 with oxirane 3 of Chart No. 8, failed.

Thus, direct fusion of compounds 3 and 4 led almost exclusively to decomposition. The reaction was repeated in a variety of solvents. No reaction was observed in refluxing 1-butanol, acetonitrile or bromobenzene. In refluxing diethylbenzene (bp 180-182°C), a trace spot for a potential product was observed on TLC after 88 hours along with unreacted starting material and polar decomposition products. In the presence of cobalt chloride or lithium triflate as catalysts, no reaction was observed at room temperature and decomposition of the oxirane took place at elevated temperatures.

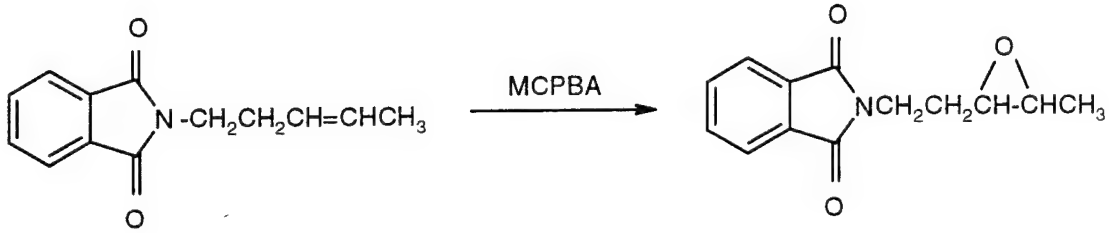
In view of this, the oxirane was treated with sodium iodide-acetic acid to give a mixture of two products, the isomeric iodohydrins. Separation of these products was initiated but at the request of the COR, all work on this assignment was suspended.

CHART NO. 8

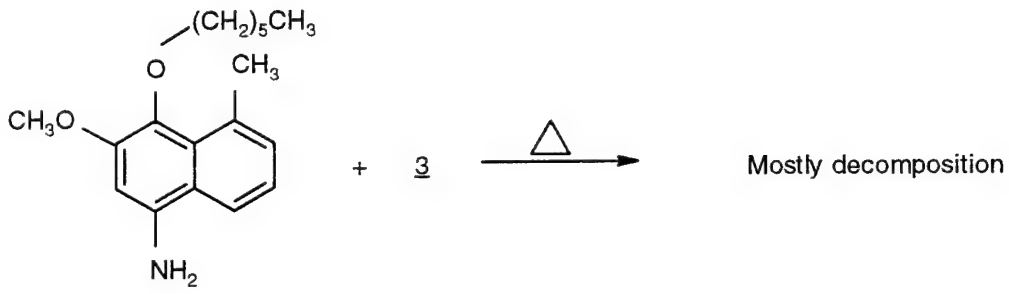
8-[(4-AMINO-2-HYDROXY-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY)-6-METHOXY-4-METHYLQUINOLINE



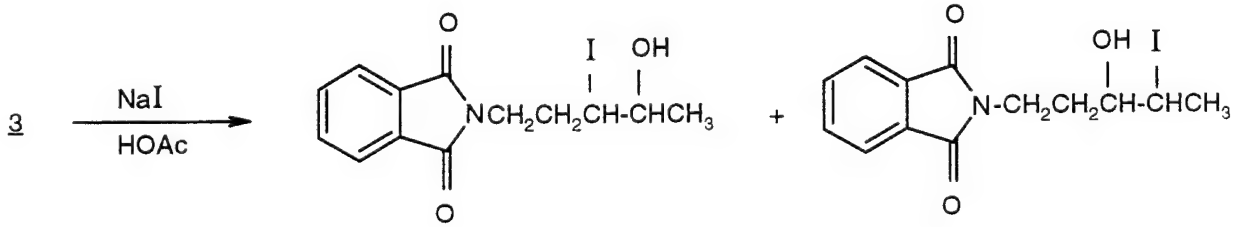
1



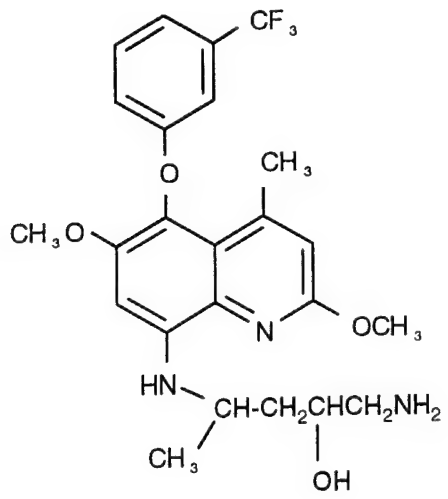
2 3



4



3.2 8-[(4-Amino-3-hydroxy-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline



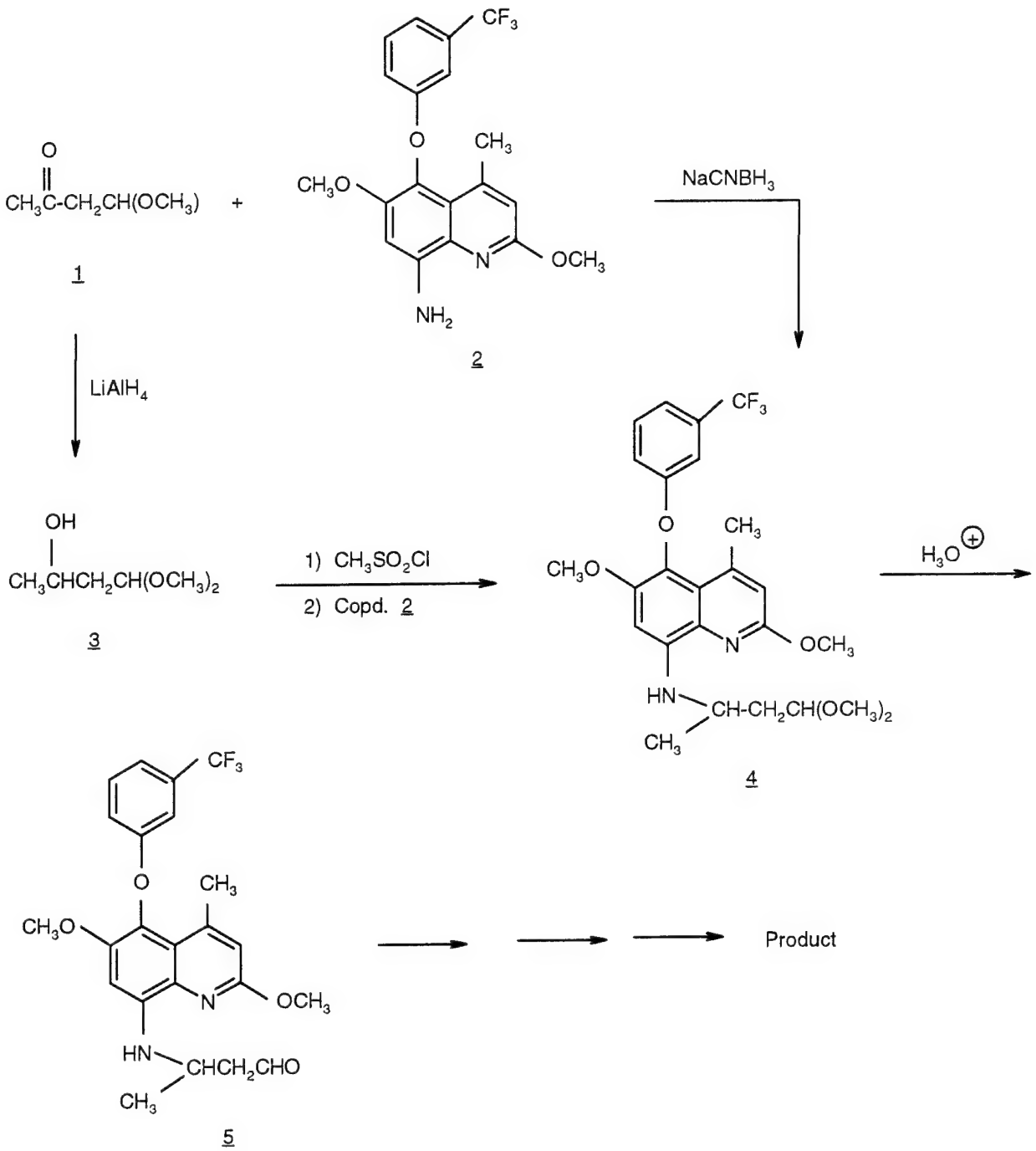
A potential route to the title compound is shown in Chart No. 9.

The initial approach involved reductive alkylation of quinoline 2 with acetylacetaldehyde dimethyl acetal. No reaction took place in methanol solvent but product formation was observed in acetonitrile solvent in the presence of acetic acid. Workup of the reaction mixture led to the isolation of a compound identified by NMR and elemental analysis as the alkylated quinoline 4.

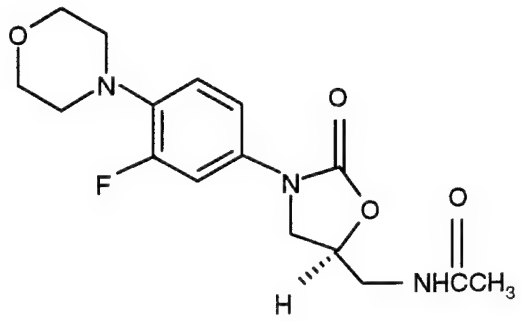
As another approach, compound 1 was reduced with lithium aluminum hydride to alcohol 3 which was treated successively with triflic anhydride and quinoline 2. Product formation was observed but the reaction did not go to completion. Alternatively, compound 3 was converted to the more stable methanesulfonate ester and coupled with quinoline 2 to give intermediate 4. Hydrolysis of the acetal will be investigated next.

CHART NO. 9

8-[(4-AMINO-3-HYDROXY-1-METHYLBUTYL)AMINO]-2,6-DIMETHOXY-4-METHYL-5-[3-(TRIFLUOROMETHYL)PHENOXY]QUINOLINE

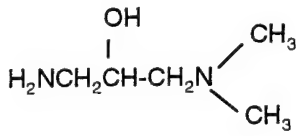


3.3 (S)-N-[[3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide



Synthesis of the title compound by the route shown in Chart No. 10 was completed. Characterization of the final product is in progress.

3.4 1-Amino-3-dimethylamino-2-propanol



Preparation of the title compound by the route shown in Chart No. 11 is in progress.

Thus, a sample of commercial epoxide 1 was treated with ethanolic dimethylamine to give, after chromatography, a sample of pure intermediate 2. Acid hydrolysis of compound 2 will give the product amine dihydrochloride salt which will be converted to the free base with ion exchange resin and purified by distillation.

Since a sufficient quantity of compound 1 could not be purchased (out of stock), the necessary starting materials have been ordered and the compound will be prepared in-house.

CHART NO. 10

(S)-N-[[3-(3-FLUORO-4-MORPHOLINYLPHENYL)-2-OXO-5-OXAZOLIDINYL]METHYL]ACETAMIDE

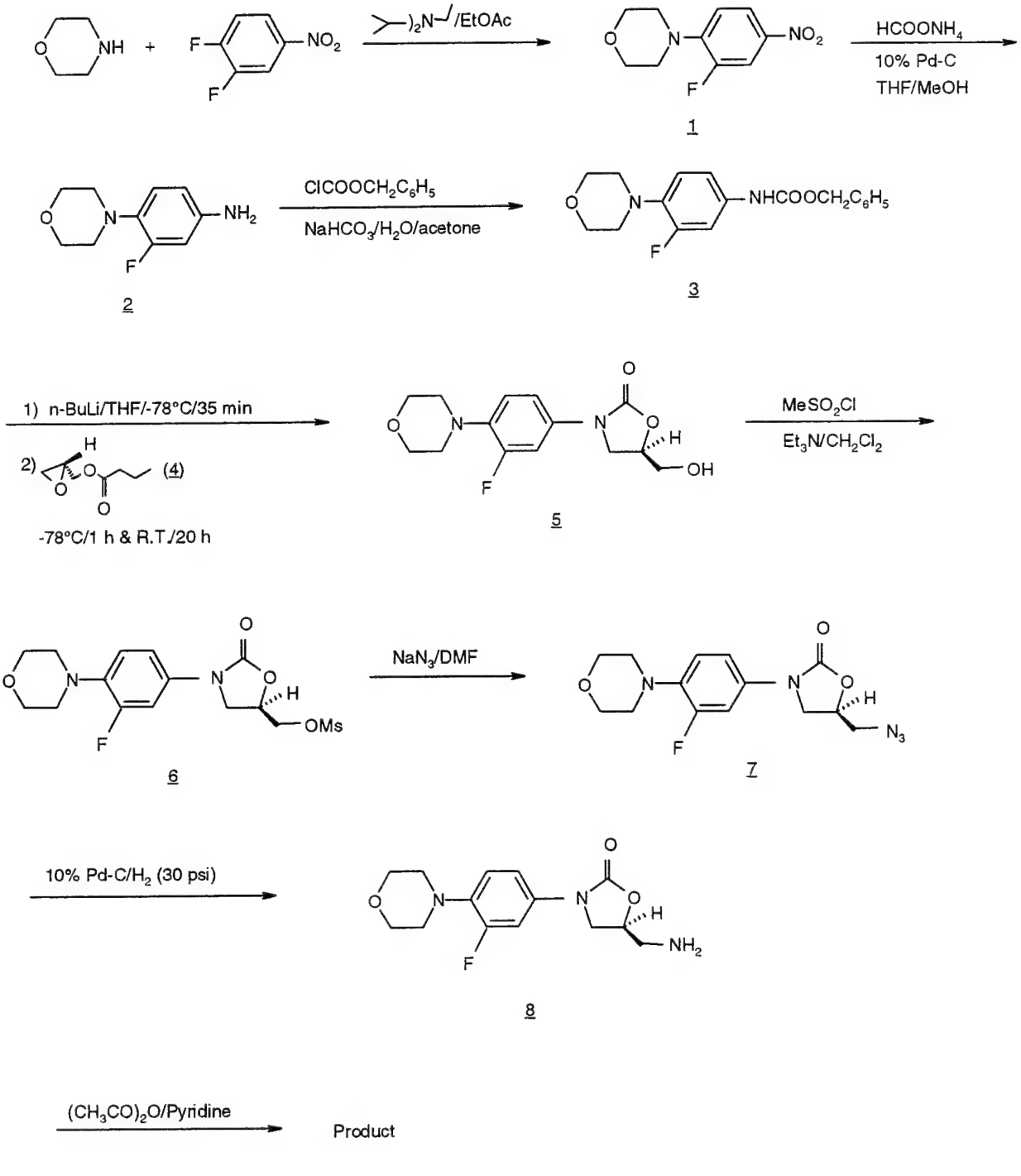
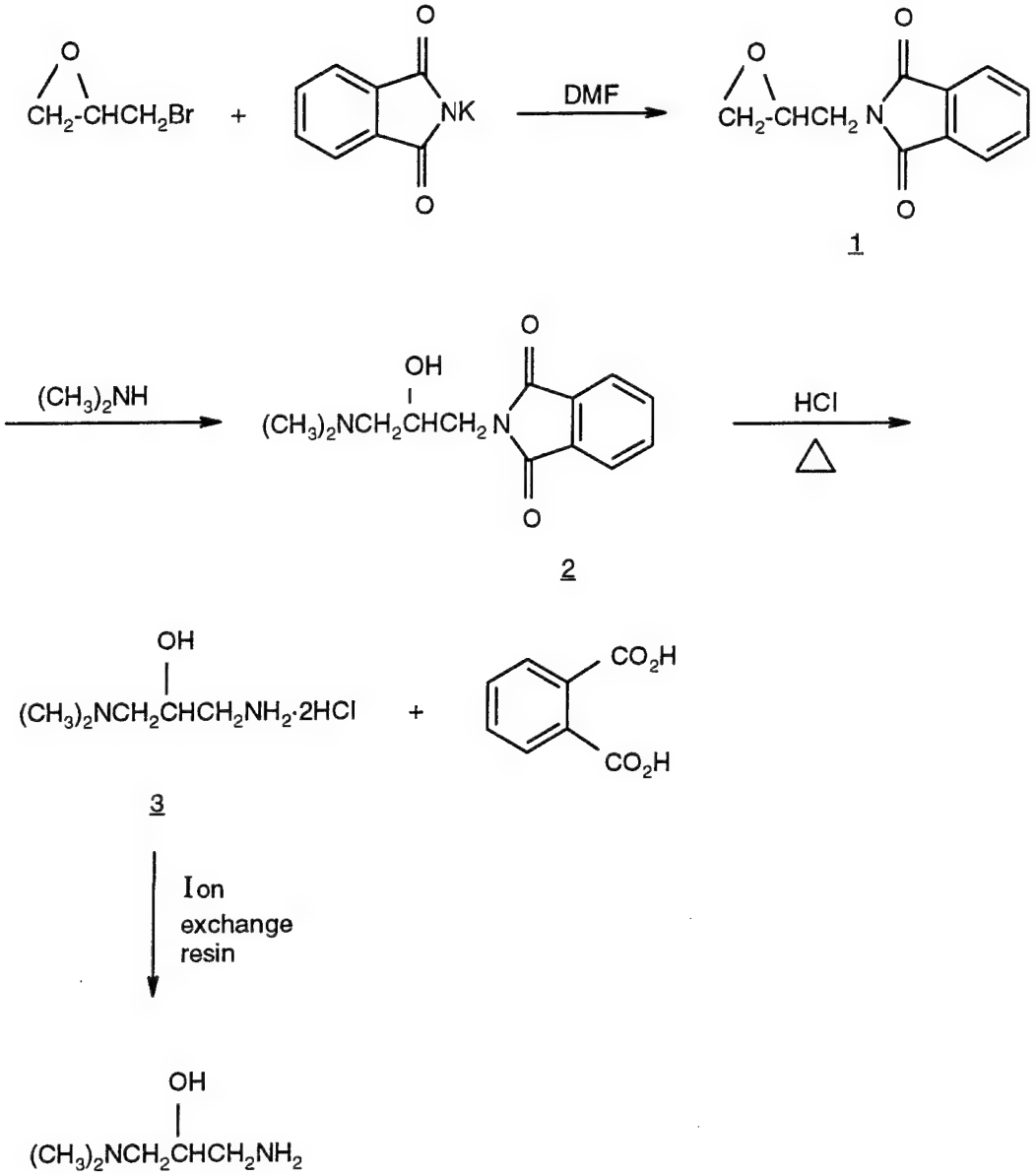
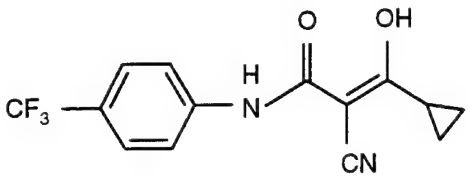


CHART NO. 11

1-AMINO-3-DIMETHYLAMINO-2-PROPANOL

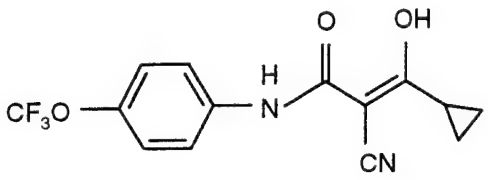


3.5 2-Cyano-3-cyclopropyl-3-hydroxy-N-[4-(trifluoromethyl)-phenyl]propenamide



No work was done on this assignment.

3.6 2-Cyano-3-cyclopropyl-3-hydroxy-N-[4-(trifluoro-methoxy)phenyl]propenamide



No work was done on this assignment.

4. EXPERIMENTAL

All melting and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1310 Spectrometer. Elemental analysis were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Vapor phase chromatography was performed on a Hewlett-Packard HP5890A instrument with HP3394A integrator/recorder. High pressure liquid chromatography was performed using a Beckman Model 110B solvent delivery module and LDC 3100 variable wavelength detector with HP3394A integrator/recorder. NMR spectra were determined on a Nicolet QE 300 Spectrometer. Optical rotations were determined on a Jasco Model DIP-370 digital polarimeter.

4.1 (R)-(-)- And (S)-(+)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline

Preparation of the title compounds by resolution of racemic WR 242511 is described in section 4.1.1, the asymmetrical synthesis is described in section 4.1.2 and determination of optical purity in section 4.1.3. Preparation of racemic WR 242511 has been described in two previous reports (5,8).

4.1.1 Resolution of WR 242511

(R)(-)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline hemisuccinate (WR 280510): - A solution of dl-8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (44.9 g, 0.12 mol) in isopropanol (100 mL) was added to a solution of dibenzoyl-L-tartaric acid monohydrate (45.2 g, 0.12 mol) in isopropanol (225 mL). The mixture was heated to obtain a clear solution, then stored at room temperature over the weekend. The precipitate was collected by filtration to give 44.1 g of yellow, crystalline tartrate salt, mp 155-156°C (dec). The salt was recrystallized from 95% aq. ethanol (185 mL) by allowing the solution to stand at room temperature overnight to give 38.7 g of salt, mp 161-163°C (dec). (The filtrates from the two recrystallizations were combined, filtrate A, and saved for preparation of the other enantiomer.) The salt (38.7 g) was recrystallized two more times from 95% aq. ethanol to give 31.4 g of partially resolved salt. At this point it was determined that the title quinoline forms hemi-salt with dibenzoyl-L-tartaric acid. Therefore, the salt (29.8 g) was basified by passage of a methanol solution through a Dowex 2-X8 ion-exchange resin to give 19.7 g of the quinoline base as a brown oil. To a solution of this oil (19.7 g, 52.7 mmol) in isopropanol (100 mL) was added a solution of dibenzoyl-L-tartaric acid monohydrate (9.9 g, 26.4 mmol) in isopropanol (30 mL). The solution was stored at room temperature overnight. The solid was collected by filtration to give 28.3 g of product, mp 156-157°C (dec). This material (26.5 g) was dissolved in warm methanol (400 mL). The solution was filtered through a pad of celite and

the filtrate was concentrated (aspirator) to dryness. The residue was dissolved in hot 95% ethanol (500 mL) and the clear solution was allowed to stand at room temperature overnight. Filtration of the mixture gave 12.3 g of salt, mp 161.5-163.5°C (dec). Concentration of the filtrate gave a second crop, 4.6 g, mp 159-160°C (dec). One recrystallization of the second crop (4.6 g) from 95% aq. ethanol gave 1.5 g of salt, mp 162-164°C (dec). The combined salt (12.3 g, + 1.5 g) was recrystallized from 95% ethanol (250 mL) to give 9.5 g of product, mp 165-167°C (dec). One more recrystallization gave 8.1 g of pure salt as yellow crystals, mp 166-168°C (dec). (All of these filtrates were combined, filtrate B, and saved for preparation of the other enantiomer). The pure salt (7.9 g) was dissolved in methanol and passed through a column of Dowex 2-X8 ion exchange resin (base form, 100 mL, 1.2 meq/mL). Concentration of the eluate gave title quinoline free base, 5.3 g, in the form of a clear yellow oil, $[\alpha]^{25}_{D}$ -30.5° (c, 3.51, EtOH). The free base (5.3 g, 14.2 mmol) was dissolved in warm acetonitrile (40 mL), and the solution was treated with a warm solution of succinic acid (0.84 g, 7.1 mmol) in isopropanol-acetonitrile (1:1, 40 mL). A yellow precipitate formed immediately but it dissolved when the addition was completed. The solution was stirred at room temperature for 30 min then refrigerated overnight. The resulting mixture was filtered to give 5.9 g of the hemisuccinate salt, mp 127-128°C. The salt was dissolved in warm isopropanol (60 mL) and the solution was filtered. The clear filtrate was stirred at room temperature. When crystal formation began, warm acetonitrile (60 mL) was added slowly. The mixture was stirred at room temperature for 3 h, then refrigerated overnight. The product was collected by suction filtration and dried at 75°C/0.2 mmHg for 4 h to give 5.5 g of pure target compound as yellow crystals, mp 127-129°C; $[\alpha]^{25}_{D}$ -29.3° (c, 1.12, MeOH). ^{1}H NMR (DMSO-d_6) δ 8.36 (d, J=4.1 Hz, 1 H), 7.18 (dd, J=0.8, 4.1 Hz, 1 H) 6.56 (s, 1 H), 6.09 (d, J=8.8 Hz, 1 H), 3.90 (s, 3 H), 3.81 (t, J=6.5 Hz, 2 H), 3.71 (m, 1 H), 2.79 (s, 3 H), 2.63-2.71 (m, 2 H), 2.24 (s, 2 H), 1.42-1.75 (m, 8 H), 1.31-1.35 (m, 4 H), 1.22 (d, J=6.2 Hz, 3 H), 0.89 (t, J=6.8 Hz, 3 H).

Anal. Calcd for $C_{22}H_{35}N_3O_2 \cdot 1/2\ C_4H_6O_4$ (432.59): C, 66.64; H, 8.85; N, 9.71. Found: C, 66.74; H, 8.99; N, 9.72.

Thin-Layer Chromatography Analtech HPTLC-RPSF

Eluent	Rf	Comment
0.2 M NaH_2PO_4-MeOH (1:9)	0.40	Homogeneous

(S)(+)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline hemisuccinate (WR 280511): - The mother liquors from the first two crystallizations of the L-salt (filtrate A) were concentrated (aspirator) to dryness. The residue was dissolved in a mixture of toluene (200 mL) and 2 N NaOH (200 mL). The aqueous layer was separated and extracted with methylene chloride (1 x 200 mL). The two organic layers were washed separately with brine (2 x 200 mL), then they were combined, dried (K_2CO_3), and filtered. The filtrate was treated with charcoal (5 g) and filtered through a celite pad. The filtrate was concentrated (aspirator, then vacuum pump) to give 17 g of partially resolved quinoline free base as a thick brown oil. A solution of this oil (17 g, 45.5 mmol) in isopropanol (30 mL) was added to a hot solution of dibenzoyl-D-tartaric acid (16.3 g, 45.5 mmol) in isopropanol (80 mL). The solution was allowed to stand at room temperature over the weekend. The mixture was filtered to give 18 g of a brown solid, mp 140-145°C (dec). One recrystallization from 95% ethanol (50 mL) gave yellow crystals, 11 g, mp 161-163°C (dec); $[\alpha]^{25}_D$ + 60.4° (c, 1.28, MeOH). The filtrates from the two recrystallization were combined and concentrated (aspirator) to dryness. The residue was basified (Dowex resin) and treated with dibenzoyl-D-tartaric acid (4.5 g) to give 6 g of salt, mp 155-157°C (dec); $[\alpha]^{25}_D$ + 50.6° (c, 1.79, MeOH). The remaining mother liquors from the L-salt (filtrate B) were treated in a similar manner to give 12.1 g of the D-salt, mp 160-162°C (dec); $[\alpha]^{25}_D$ + 50.0° (c, 1.47, MeOH). The latter two crops (6 g and 12.1 g) were combined and recrystallized from ethanol (200 mL) to give 9.6 g of product, mp 159-161°C (dec). One more recrystallization from ethanol (150 mL) gave 6.0 g of salt, mp 164-166°C (dec); $[\alpha]^{25}_D$ + 60.8° (c, 1.19, MeOH).

This material was combined with 10 g of the above 11 g crop and recrystallized from ethanol (200 mL) to give 12.5 g of salt, mp 164-167°C (dec). A final recrystallization from ethanol (160 mL) gave 11 g of pure dibenzoyl-D-tartaric acid salt, mp 166-168°C (dec). A solution of the salt (10.8 g) in methanol was passed through a column of Dowex 2-X8 ion exchange resin (base form, 130 mL, 1.2 meq/mL, 2.2 cm x 48 cm column) and the resin was washed with methanol. The product-containing fractions were combined and concentrated (aspirator, then vacuum pump) to give 7.2 g of pure quinoline base, $[\alpha]^{25}_D$ + 31.2° (c 3.65, EtOH). A warm solution of succinic acid (1.14 g, 9.6 mmol) in a mixture of acetonitrile (25 mL) and isopropanol (25 mL) was added slowly to a stirred solution of the quinoline free base (7.2 g, 19.3 mmol) in acetonitrile (50 mL). A yellow precipitate formed initially but dissolved when the addition was completed. The mixture was stirred at room temperature for 30 min, then refrigerated overnight. The solid was collected by filtration to give 8 g of shiny yellow crystals, mp 127-128°C. The solid (8 g) was dissolved in warm isopropanol (80 mL) and the solution was filtered. The clear filtrate was stirred at room temperature

until crystals began to form, then warm acetonitrile (80 mL) was added slowly. The mixture was stirred at room temperature for 3 h and with ice-cooling for 3 h. The solid was collected by filtration and dried at 75°C/0.5 mmHg for 4 h to give 7.5 g of pure product, mp 127-129°C; $[\alpha]^{25}_{D}$ + 30.0° (c 1.14, MeOH). ^{1}H NMR (DMSO-d_6) δ 8.36 (d, J=4.2 Hz, 1 H), 7.18 (dd, J=0.7, 4.3 Hz, 1 H), 6.56 (s, 1 H), 6.09 (d, J=9.4 Hz, 1 H), 3.90 (s, 3 H), 3.81 (t, J=6.5 Hz, 2 H), 3.71 (m, 1 H), 2.79 (s, 3 H), 2.67-2.71 (m, 2 H), 2.24 (s, 2 H), 1.42-1.75 (m, 8 H), 1.31-1.35 (m, 4 H), 1.22 (d, J=6.2 Hz, 3 H), 0.89 (t, J=7.0 Hz, 3 H).

Anal. Calcd for $C_{22}H_{35}N_3O_2 \cdot 1/2\ C_4H_6O_4$ (432.59): C, 66.64; H, 8.85; N, 9.71. Found: C, 66.81; H, 9.07; N, 9.80.

Thin-Layer Chromatography Analtech HPTLC-RPSF

Eluent	Rf	Comment
0.2 M NaH_2PO_4-methanol (1:9)	0.40	Homogeneous

Materials

WR 242511	Ash Stevens Inc., Lot No. CT-6-233
Isopropanol	Chempure, Lot No. M158KLW
Dibenzoyl-L-tartaric acid monohydrate	Aldrich, Lot Nos. LG10128TX and EP02429JM
Dibenzoyl-D-tartaric acid	Aldrich, Lot No. CN15007CM
Ethanol	VWR Scientific, Lot No. 9504125
Methanol	J.T. Baker, Lot No. H47611
Celite	Celite Corporation, Lot No. 94024
Dowex 2-X8 resin (washed (with base prior to use)	Bio-Rad Laboratories Inc., Lot No. M4738D
Acetonitrile	Aldrich, Lot No. 00418TW
Succinic acid	Aldrich, Lot No. EG16616CG

4.1.2 Asymmetric synthesis of the S-(+) enantiomer

The synthesis route is shown in Chart No. 1. Preparation of the optically active sulfonate ester 5 was described in the previous report (1).

A mixture of 8-amino-5-hexyloxy-6-methoxy-4-methylquinoline (1.01 g, 3.5 mmol), (R)(-)-4-[(3-nitrophenyl)sulfonyloxy]-1-phthalimidopentane (5) (1.46 g, 3.5 mmol), diisopropylamine (0.35 g, 3.5 mmol), and acetonitrile (7 mL) was heated at reflux for 20 h. Additional sulfonate 5 (1.46 g) and diisopropylamine (0.35 g) were added and heating was continued for 4 h. The mixture was cooled, diluted with water (4 mL) and extracted with methylene chloride (2 x 7 mL). The combined extract was washed with

saturated aq. $NaHCO_3$ (7 mL), brine (7 mL), then it was dried ($MgSO_4$) and filtered. The filtrate was concentrated (aspirator) and the residue was chromatographed twice over silica gel (1 x 70 g, 1 x 100 g) eluting with toluene-ether (4:1). Fractions containing pure product 6 were combined and concentrated to give a clear, light brown, thick oil (402 mg), $[\alpha]^{25}_D$ + 8.76 (c 8.04, EtOH). The infrared spectrum and TLC behavior of this compound were identical with those of the authentic dl-compound. Other fractions containing product and impurities were also combined and concentrated to give 613 mg of impure product which was set aside. A mixture of the pure product 6 (402 mg, 0.79 mmol), anhydrous hydrazine (101 mg, 3.16 mmol), and ethanol (8 mL) was heated at reflux for 3 h. The mixture was cooled to 40°C and filtered. The solid was washed with ethanol (5 x 2 mL) and discarded. The combined filtrate was concentrated (aspirator) to a volume of ca. 10 mL, diluted with water (10 mL) and extracted with methylene chloride (2 x 20 mL). The combined extract was washed with aq. 25% KOH (3 x 10 mL), brine (3 x 10 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated and the residue was dissolved in EtOH (10 mL). The solution was stirred with charcoal (0.2 g) and filtered through a celite pad. The filtrate was concentrated (aspirator, then vacuum pump) to give 251 mg of pure compound 7 as yellow clear oil, $[\alpha]^{25}_D$ + 8.27° (c 5.02, EtOH). The IR spectrum and TLC behavior of this material were identical to those of authentic WR 242511 free base.

Materials

8-Amino-5-hexyloxy-6-methoxy-4-methylquinoline	Ash Stevens Inc., Lot No. KB-02-59
(R)(-)-4-[(3-nitrophenyl)-sulfonyloxy]-1-phthalimido-pentane	Ash Stevens Inc., Lot No. CT-6-129
Diisopropylamine	Fluka, Lot No. 327045-1-994
Acetonitrile	Aldrich, Lot No. 00418TW
Methylene chloride	J.T. Baker, Lot No. H30620
Silica gel	EM Science, Lot No. 3007201
Toluene	J.T. Baker, Lot No. H15630
Ethyl ether	Fisher Scientific, Lot No. 956050-15
Hydrazine, anhydrous	Aldrich, Lot No. 07326MF
Ethanol	VWR Scientific, Lot No. 9504125
Sodium bicarbonate	FMC Corporation, Lot No. 92-358
Potassium hydroxide	Sigma, Lot No. 22H01131
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161

4.1.3 Optical purity analysis

A solution of partially resolved WR 242511 [124 mg, 0.332 mmol, $[\alpha]^{25}_{D}$ + 4.67° (c 1.49, EtOH)] in pyridine (1 mL) was cooled to -15°C under a nitrogen atmosphere. To the solution was added (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (0.1 mL, 134 mg, 0.531 mmol). The reaction mixture was stirred at -15° to -10°C for 1.5 h, and the temperature was raised to 0°C over 1 h. After stirring at 0°C for one additional hour, the reaction mixture was quenched with water (2 mL) at 0°. The product was extracted with methylene chloride (3 x 2 mL). The combined methylene chloride extract was washed successively with saturated aq. $NaHCO_3$ (1 x 2 mL), water (3 x 2 mL), and brine (2 x 2 mL), then it was dried ($MgSO_4$) and filtered. The solution was concentrated (aspirator) to give a thick oil (115 mg). The oil was chromatographed over silica gel (12 g) and the column was eluted with ethyl acetate-hexane (1:1). The product-containing fractions were combined and concentrated to give 90 mg (46%) of pure amide in the form of a yellow thick oil. The ^{19}F NMR spectrum of this product gave two signals in the ratio of 1.37:1. Therefore, the maximum optical rotation is calculated as 29.9° (EtOH). In a similar manner, a sample of the resolved product with $[\alpha]^{25}_{D}$ -29.5° (EtOH) was converted to the amide derivative which showed only one singlet in the ^{19}F NMR.

Materials

Partially resolved WR 242521	Ash Stevens Inc., Lot No. CT-6-272
Optically pure WR 242521	Ash Stevens Inc., Lot No. CT-6-271
(+)-α-Methoxy-α-trifluoro-methylphenylacetyl chloride	Acros Organics, Lot No. 80544-1
Pyridine	Aldrich, Lot No. LW05916KW
Methylene chloride	J.T. Baker, Lot No. H40639
Sodium bicarbonate	FMC Corporation, Lot No. 92-358
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Silica gel	EM Science, Lot No. 3007201
Ethyl acetate	Fisher Scientific, Lot No. 952084
Hexanes	J.T. Baker, Lot No. D41602

4.2 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate (WR 238605)

The synthesis route to the title compound is shown in Chart No. 2.

5-Chloro-6-methoxy-4-methyl-8-nitroquinoline (1): - A 5 L 3 neck flask equipped with a temperature probe, a stirrer and a reflux condenser was charged with 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline (900 g, 3.84 mol) and phosphorus oxychloride (2.95 kg, 19.24 mol). The mixture was heated to 85°C at which point the reaction exothermed to 105°C. The mixture was cooled to 85°C and maintained at this temperature for 30 min. The mixture was allowed to cool to 60°C and poured into a rapidly stirred mixture of ice (18 kg) and water (10 L). The mixture was adjusted to pH 7-8 by the addition of 25% aq. sodium hydroxide (13.5 L), while maintaining the temperature below 20°C by the addition of ice (9 kg). The mixture was filtered and the solids were slurried with water (2 x 6 L). The solids from the last filtration were washed with water (1 L), isopropanol (2 L) and petroleum ether (3 L) and air-dried to constant weight to give 955 g of crude product.

Similar runs were made and a total of 3.96 kg of 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline was processed to give 5.19 kg of crude product 1.

The crude product (1126 g) was dissolved in refluxing methylene chloride (10 L). The solution was treated with potassium carbonate (180 g) and celite (300 g) and heated at reflux for 30 min, then it was filtered through a pad of celite. The top layer of the celite pad was slurried with methylene chloride (2 x 1.5 L) and filtered after each slurry. After the final filtration, the filter pad was washed with methylene chloride (2 L). The combined filtrate was concentrated to a volume of ca. 9 L and applied onto a column of dry silica gel (5 kg, 15 x 57 cm). The column was eluted with methylene chloride (48 L). The product-containing fractions were combined and concentrated to a slurry. The slurry was transferred to pyrex dish and air-dried to give 997 g of chromatographed product.

The remaining crude material was treated in a similar manner and gave an additional 2.74 kg of chromatographed product.

The combined chromatographed product (3.74 kg) was dissolved in refluxing toluene (15 L). The solution was allowed to cool to room temperature overnight, then it was cooled in an ice bath for 6 h. The solid was collected by filtration, washed with cold (5°C) toluene (3 L) and petroleum ether (2 L) and air-dried to give 3.44 kg of pure product, mp 168-169.5°C; lit. mp 167-169.5°C (4). The mother liquor was concentrated to give 238 g of less pure product. This material was recrystallized from toluene (1 L) to give 217 g of pure product, mp 168-169°C.

The combined yield was 3.66 kg (85%).

Anal. Calcd For $C_{11}H_9ClN_2O_3$ (252.66): C, 52.29; H, 3.59; Cl, 14.03; N, 11.09. Found (1st crop): C, 52.14; H, 3.57; Cl, 14.05; N, 11.01. Found (2nd crop): C, 52.39; H, 3.46; Cl, 13.99; N, 10.92.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Methylene chloride	0.21	Homogeneous
Ethyl acetate	0.69	Homogeneous

Materials

5-Hydroxy-6-methoxy-4-methyl-8-nitroquinoline	Ash Stevens Inc., Lot No. PAS-02-156
Phosphorus oxychloride, 99%	Aldrich, Lot No. 04003MV Rhone Poulenc, Lot No. 080220
Water, deionized	Ash Stevens Inc.
Sodium hydroxide, ACS reagent	VWR Scientific, Lot No. D43058 J.T. Baker, Lot No. H02937
Isopropanol	Fisher Scientific, Lot No. 943173
Petroleum ether (bp 50-110°C), reagent	J.T. Baker, Lot No. F40609
Petroleum ether (bp 35-60°C), reagent	J.T. Baker, Lot No. H46607
Methylene chloride, ACS reagent	J.T. Baker, Lot Nos. G18640, and H49624
Potassium carbonate, anhydrous	Johnson Mathey, Lot No. J16A15
Celite	Manville, no Lot No.
Silica gel, 70-230 mesh	EM Science, Lot No. 33015
Toluene, ACS reagent	Mallinckrodt, Lot No. 8608KMAE

6-Methoxy-4-methyl-8-nitro-5-(3-trifluoromethylphenoxy)-quinoline (2): - A 12 L 3 neck flask equipped with an addition funnel, a stirrer, a temperature probe, and a distillation head was charged with 2-ethoxyethanol (3.1 L) and m-hydroxybenzotrifluoride (708 g, 4.37 mol). The solution was purged with nitrogen and compound 1 (788 g, 3.12 mol) was added. The mixture was blanketed with nitrogen and heated to 127°C. A hot (85-90°C) solution of potassium hydroxide (257 g, 3.89 mol) in 2-ethoxyethanol (1.5 L) was prepared separately under a nitrogen atmosphere, then it was added over a 25 min period to the reaction mixture while maintaining the temperature at 127-132°C. During the addition, a portion of the solvent boiling below 127°C was removed by distillation. After the addition was completed, the mixture was maintained at 130-133°C for 90 min while additional low boiling solvent was removed by distillation (total

solvent removed was 1.3 L). The reaction mixture was cooled to room temperature, methanol (3.1 L) was added and the mixture was stirred and cooled in an ice bath for 2 h. The mixture was filtered and the solid was washed with cold (5°C) ethanol (3 x 500 mL). The damp filter cake was slurried with water (4.7 L) and the mixture was filtered. The solid was washed with water (2 x 1.1 L), cold ethanol (3 x 500 mL) and petroleum ether (2 x 600 mL) and air-dried to yield 869 g of crude product 2.

Similar runs were made and from 3.64 kg of compound 1 there was obtained 4.01 kg of crude product 2.

Crude product 2 (4.01 kg) was dissolved in refluxing toluene (40 L). Norit A (250 g) was added and after a 10 min reflux, the mixture was filtered through a pad of celite. The filter pad was washed with boiling toluene (1.5 L). The stirred filtrate was allowed to cool to room temperature overnight, then it was cooled in an ice bath for 3.5 h. The solid was collected by filtration, washed with cold (5°C) toluene (2.5 L), ethanol (2 L) and petroleum ether (1.5 L), and air-dried to yield 3.76 kg (69%) of pure compound 2, mp 213-214°C; lit., mp 213-217°C (4), mp 208-210°C (16).

Anal. Calcd for $C_{18}H_{13}F_3N_2O_4$ (378.31): C, 57.15; H, 3.46; F, 15.07; N, 7.40. Found: C, 57.12; H, 3.46; F, 15.12; N, 7.41.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Methylene chloride	0.20	Homogeneous
Ethyl acetate	0.71	Homogeneous

Materials

Compound 1	Ash Stevens Inc., Lot Nos. KB-02-78 and KB-02-79
2-Ethoxyethanol, reagent	J.T. Baker, Lot Nos. F27621 and H02619
m-Hydroxybenzotrifluoride	Marshallton, Lot No. 28-078
Potassium hydroxide, 85+%, ACS reagent	Aldrich, Lot No. 03408JG
Methanol	Ashland, Lot No. 0720410
Ethanol, reagent 200 proof	Aaper Alcohol, Lot No. 95A24QA-RA
Petroleum ether, bp 35-60°C, ACS	J.T. Baker, Lot No. H46607

Materials (Continued)

Water, deionized	Ash Stevens Inc.
Toluene, ACS reagent	Malinckrodt, Lot No. 8608KMAE
Norit A, acid washed	Pfanstiehl Laboratories Inc., Lot No. 16055
Celite	Manville, no Lot No.

8-Amino-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)-quinoline (3): - A 12 L three-neck flask equipped with an addition funnel, a stirrer, a reflux condenser, and a temperature probe was charged with compound 2 (1.00 kg, 2.64 mol), iron filings (680 g), butyl ether (400 mL) and water (2.2 L). The stirred mixture was heated to 88°C and a solution of acetic acid (180 mL) in water (1.44 L) was added over a 15-20 min period. The mixture was heated at 93-95°C for 40 min, more iron filings (174 g) were added and heating was continued for 40 min when additional acetic acid (240 mL) in water (1.44 L) was added. After a further 30 min at 93-95°C, analysis by thin-layer chromatography showed no starting material remaining. The mixture was cooled to 40-50°C and extracted by decantation with hot ethyl acetate (4 L, 2 x 3 L, 2 L). The combined extract was filtered through a pad of celite and the filtrate was washed with saturated aqueous sodium bicarbonate (2 x 1.35 L) and water (2 x 1.65 L). The organic layer was dried over magnesium sulfate (500 g), filtered, and the filtrate was concentrated to dryness to give 915 g of crude product.

Similar runs were made and a total of 3.75 kg of compound 2 was processed to give 3.33 kg of crude product 3.

Crude compound 3 (3.33 kg) was dissolved in boiling cyclohexane (35 L). The solution was treated with Norit A (775 g), heated at reflux for 15 min, and filtered through a pad of celite. Washing with boiling cyclohexane was attempted but the funnel plugged up. The filter pad was extracted with boiling cyclohexane (6 L) and the mixture was filtered through a pad of celite. The celite pad was washed with boiling cyclohexane (2 L). The plugged funnel was washed with ethyl acetate (2 L) and the wash was saved (see below). The two cyclohexane filtrates were allowed to cool to room temperature overnight, then they were cooled to 10°C. The solid from both filtrates was collected together, washed with cold (10°C) cyclohexane (4 L) and petroleum ether (5 L) and air-dried to give 2.75 kg of pure product 3, mp 114-116°C; lit., mp 115-117.5°C (4), mp 116-117°C (16).

The ethyl acetate wash from above was filtered through a pad of celite and the filter pad was washed with ethyl acetate (500 mL). The combined filtrate was concentrated to dryness to give 220 g of crude product. This material was recrystallized from cyclohexane (1 L) to give 209 g of pure compound 3, mp 114-116°C.

The combined cyclohexane mother liquors were concentrated to a volume of ca. 2.5 L and cooled to 10°C. The solid was collected by filtration to give 128 g of a less pure second crop. This material was recrystallized from cyclohexane (1.3 L) to give 118 g of pure compound 3, mp 114-116°C.

The combined yield of pure product 3 was 3.08 kg (89%).

^{1}H NMR (DMSO-d_6) δ 8.39 (d, J=4.2 Hz, 1 H, H-2), 7.46 (app t, J=8.1 Hz and 7.8 Hz, 1 H, H-5'), 7.28 (d, J=7.8 Hz, 1 H, H-4'), 7.15 (d, J=4.2 Hz, 1 H, H-3), 7.01 (s, 1 H, H-2'), 6.97 (d, J=8.4 Hz, 1 H, H-6'), 6.88 (s, 1 H, H-7), 6.12 (s, 2 H, NH_2), 3.71 (s, 3 H, OCH_3), 2.49 (s, 3 H, ArCH_3).

Anal. Calcd for $C_{18}H_{15}F_3N_2O_2$ (348.32): C, 62.07; H, 4.34; F, 16.36; N, 8.04. Found (KB-02-93): C, 61.86; H, 4.33; F, 16.37; N, 7.97. Found (KB-02-94A): C, 61.89; H, 4.42; F, 16.45; N, 8.07. Found (KB-02-94B): C, 61.89; H, 4.45; F, 16.45; N, 8.03.

Thin-Layer Chromatography EM Science Silica Gel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate	0.62	Homogeneous
Toluene-acetone-triethylamine (70:19:5)	0.47 0.26	Major trace Trace

Materials

Compound 2	Ash Stevens Inc., Lot No. KB-02-86
Iron filings, 40 mesh	MCB, Lot No. 3H17
	Fisher Scientific, Lot No. 947501
Butyl ether, 99%	Aldrich, Lot Nos. 13909CF and 01702KX
Water, deionized	Ash Stevens Inc.
Acetic acid, ACS reagent	Ashland, Lot No. 030923E
Ethyl acetate, ACS reagent	J.T. Baker, Lot No. H48640
Celite	Manville, no Lot No.
Sodium bicarbonate, ACS reagent	Spectrum Chemical Corp., Lot No. IB155
Magnesium sulfate, anhydrous	Spectrum Chemical Corp., Lot No. HF161
Cyclohexane, ACS reagent	J.T. Baker, Lot No. 429331
Norit A, acid washed	Pfanstiehl Laboratories Inc., Lot No. 16055
Petroleum ether (bp 35-60°C), ACS	J.T. Baker, Lot No. H46607

6-Methoxy-4-methyl-8-phthalimido-5-(3-trifluoromethy-phenoxy)quinoline (4): - A 50 L three-neck flask equipped with a temperature probe, a stirrer, and a Dean-Stark trap was charged with toluene (9 L), xylenes (9 L) and phthalic anhydride (677 g, 4.57 mol) and the stirred mixture was heated to 80°C. Solid product 3 (1.53 kg, 4.39 mol) was added and the mixture was heated at reflux (122-123°C) for 5 h. The water generated in the reaction (77 mL) was collected in the Dean-Stark trap. The reaction mixture was allowed to cool to room temperature overnight, then cooled in an ice bath for 3 h. The solid was collected by filtration, washed with cold (5°C) toluene (3 L) and petroleum ether (3 L) and air-dried to give 2.06 kg of pure product 4, mp 232-233°C; lit., mp 231-235°C (4), mp 228-231°C (17). The reaction was repeated on the same scale and gave 2.06 kg of pure product 4, mp 232-233°C. The combined yield was 4.12 kg (98%).

^{1}H NMR (DMSO-d_6) δ 8.55 (d, J=4.2 Hz, 1 H, H-2), 8.16 (s, 1 H, H-7), 8.1-7.9 (m, 4 H, phthalimide), 7.56 (t, J=8.1 hz, 1 H, H-5'), 7.41 (d, J=7.8 Hz, 1 H, H-4'), 7.34 (d, J=4.2 Hz, 1 H, H-3), 7.24 (s, 1 H, H-2'), 7.03 (dd, J=8.4 Hz, 2.1 Hz, 1 H, H-6'), 3.80 (s, 3 H, OCH_3), 2.64 (s, 3 H, ArCH_3).

Anal. Calcd for $C_{26}H_{17}F_3N_2O_4$ (478.43): C, 65.27; H, 3.58; F, 11.91; N, 5.86. Found (KB-02-96): C, 65.12; H, 3.37; F, 12.07; N, 5.82. Found (KB-02-97): C, 65.10; H, 3.41; F, 11.84; N, 5.81.

Thin-Layer Chromatography EM Science Silica Gel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate	0.64	Homogeneous
Toluene-methanol (4:1)	0.68	Homogeneous

Materials

Compound 3	Ash Stevens Inc., Lot Nos. KB-02-93, KB-02-94A and KB-02-94B
Toluene, ACS reagent	Mallinckrodt, Lot No. 8608KMAE
Xylenes, ACS reagent	Spectrum Chemical Corp., Lot No. GG375
Phthalic anhydride, ACS reagent	Acros, Lot No. B0029392
Petroleum ether (bp 35-60°C) ACS	J.T. Baker, Lot No. H46607

6-Methoxy-4-methyl-8-phthalimido-5-(3-trifluoromethyl-phenoxy)quinoline-1-oxide ethanolate (5): - A 50 L three-neck flask equipped with an addition funnel, a stirrer, and a reflux condenser was charged with chloroform (20.5 L) and compound 4 (2.04 kg, 4.26 mol) and the mixture was heated to reflux. 3-Chloroperoxybenzoic acid (1.79 kg, 7.26 mol based on 70% purity) was dissolved separately in hot chloroform (9 L). The layers were separated and the organic layer was dried over magnesium sulfate (86 g) and filtered. The solid was washed with chloroform (500 mL) and the combined filtrate was added over a 10-min period to the above-prepared refluxing solution of compound 4 in chloroform. The reaction mixture was heated at reflux for 2.5 h, cooled to room temperature and washed successively with 15% aqueous potassium carbonate (2 x 9.5 L) and water (10 L). The organic layer was treated with potassium carbonate (1 kg) and Norit A (200 g) and stirred at room temperature overnight. The mixture was filtered through a pad of celite and the filter pad was washed with chloroform (1.5 L). The combined filtrate was concentrated to dryness to give 2.825 kg of solid residue. The solid was triturated with hot ethanol (5.8 L) and the mixture was allowed to cool for 1 h, then it was cooled in an ice bath for 2 h. The solid was collected by filtration, washed with cold ethanol (2.5 L) and petroleum ether (2 L), and air-dried to give 1.975 kg of crude product 5.

The reaction was repeated using 2.05 kg of compound 4 and gave 1.983 kg of crude product 5. The water washes from the original reaction mixture deposited a small chloroform layer. The layers were separated and the chloroform layer was concentrated to dryness to give additional solid product. The solid was triturated with ethanol to yield 103 g of crude product 5.

The combined crude product (4.06 kg) was charged into a 100 gallon stainless steel reactor containing ethanol (126 L). The mixture was heated to reflux and allowed to cool to room temperature overnight. Next day the contents were cooled to 3°C and filtered. The solid was washed with cold ethanol (5 L) and petroleum ether (5 L) and air-dried to give 3.42 kg of recrystallized product 5. TLC analysis showed that this material now contained a new impurity. Accordingly, the compound was purified further as follows.

Recrystallized compound 5 (950 g) was dissolved in a hot mixture of toluene (5.7 L) and ethanol (0.95 L). The solution was seeded with pure product 5 and allowed to stand undisturbed at room temperature overnight. Next day the mixture was filtered. The solid was washed with toluene (1 L) and petroleum ether (1 L) and air-dried to give 586 g of purified product 5, mp 233-233.5°C.

Additional impure product (2.45 kg) was treated in a similar manner and gave 1.50 kg of purified product 5.

The toluene-ethanol mother liquor was processed further. Thus, a portion of the mother liquor (8 L) was concentrated to one-half volume. Silica gel (1.1 kg) was added and the mixture was stirred for 15 min. The solvent was decanted and the silica gel was placed on top of a chromatography column containing silica gel (0.9 kg, 8 x 34 cm column) packed in toluene. The column was eluated with toluene (5 L), toluene-ethyl acetate (9:1, 10 L; 3:1, 20 L; 1:1, 30 L; 1:3, 15 L), and ethyl acetate (5 L). The product-containing fractions were concentrated to dryness to give 160 g of purified product 5, mp 232-232.5°C. The remaining mother liquor was processed in a similar manner and gave 469 g of purified product.

The combined purified product (2.71 kg) was slurried with ethanol (5 L) and the mixture was filtered. The solid was washed with ethanol (2 L) and petroleum ether (1.5 L) and air-dried to give 2.70 kg (58%) of pure product 5, mp 233.5-234.5°C; lit., mp 233-234°C (4), mp 236-237°C (17). ^{1}H NMR (DMSO-d_6) δ 8.19 (d, J=6.3 Hz, 1 H, H-2), 8.00 (s, 1 H, H-7), 8.0-7.9 (m, 4 H, phthalimide), 7.55 (t, J=8.1 Hz, 1 H, H-5′), 7.43 (d, J=7.5 Hz, 1 H, H-4′), 7.28 (br s, 1 H, H-2′), 7.21 (d, J=6.9 Hz, 1 H, H-3), 7.06 (dd, J=8.4 and 2.1 Hz, 1 H, H-6′), 4.34 (t, J=5.1 Hz, 1 H, OH), 3.80 (s, 3 H, OCH_3), 3.42 (dq, J=5.1 and 6.9 Hz, 2 H, OCH_2), 2.56 (s, 3 H, ArCH_3), 1.02 (t, J=7.2 Hz, 3 H, CH_2CH_3).

Anal. Calcd for $C_{26}H_{17}F_3N_2O_5 \cdot C_2H_5OH$ (540.49): C, 62.22; H, 4.29; F, 10.55; N, 5.18. Found: C, 62.11; H, 4.20; F, 10.63; N, 5.25.

Thin-Layer Chromatography EM Science Silica Gel 60 F_{254}

Eluent	Rf	Comment
Toluene-methanol (5:1)	0.35	Homogeneous
Ethyl acetate	0.20	Major
	0.50	Trace
	0.64	Trace
	0.72	Trace

Materials

Compound 4	Ash Stevens Inc., Lot Nos. KB-02-96 and KB-02-97
Chloroform	J.T. Baker, Lot No. C03604
3-Chloroperoxybenzoic acid, 70-75%	Fisher Scientific, Lot No. 943340
Magnesium sulfate, anhydrous	Spectrum Chemical Corp., Lot No. KP053
Potassium carbonate, anhydrous	Spectrum Chemical Corp., Lot No. HF161
Water, deionized	Spectrum Chemical Corp., Lot No. GP011
Norit A	Ash Stevens Inc.
Celite	Pfanstiehl Laboratories Inc., Lot No. 16055
Ethanol, reagent, 190 proof	Manville, no Lot No.
Petroleum ether (bp 35-60 24°C) reagent	Aaper Alcohol, Lot No. 95D11UB-RK
Toluene, reagent	J.T. Baker, Lot Nos. H46607 and J06656
Silica gel 60, 70-250 mesh	Mallinckrodt, Lot Nos. 8608KPEZ and 8608KMAE
Ethyl acetate, ACS reagent	EM Science, Lot No. 33015
	J.T. Baker, Lot Nos. H48640 and J22613

2-Chloro-6-methoxy-4-methyl-8-phthalimido-5-(3-trifluoromethylphenoxy)quinoline (6): - A 22 L three-neck flask equipped with a stirrer, a reflux condenser and a temperature probe was charged with compound 5 (1352 g, 2.50 mol) and ethylene dichloride (8.1 L). Phosphorus oxychloride (1585 g, 10.3 mol) was added over a 30-45 min period (exotherm to 50°C). The mixture was heated at reflux for one hour at which time more phosphorus oxychloride (88 g, 0.57 mol) was added. The mixture was heated at reflux for another 30 min, then it was cooled to 10°C and poured over ice (10.8 kg). The rapidly stirred mixture was adjusted to pH 5.5 by the addition of 20% aqueous sodium hydroxide (6.5 L). Water (4 L) was added and the layers were separated. The aqueous phase was extracted with ethylene dichloride (4 x 4 L). The combined organic phase was washed with water (3 x 7.5 L) and dried over magnesium sulfate (1 kg). Sodium bicarbonate (308 g) and Norit A (405 g) were added and the mixture was stirred at room temperature overnight. Next day the mixture was filtered and the filter pad was washed with ethylene dichloride (2.6 L). The combined filtrate was concentrated to dryness (steam jet, water bath) and the residual solid was slurried with ethanol (2.3 L). The mixture was cooled in an ice bath and filtered. The solid was washed with cold ethanol (1.5 L) and petroleum ether (1.5 L) and air-dried to give 1.24 kg of crude product 6.

The reaction was repeated and 1.35 kg of compound 5 was converted to 1.23 kg of crude product 6.

The combined crude product, 2.47 kg, was dissolved in hot toluene (8.1 L). The stirred solution was allowed to cool to room temperature overnight, then it was cooled in an ice bath for 5 h. The solid was collected by filtration, washed with cold (5°C) toluene and petroleum ether (2.5 L) and air-dried to give 2.20 kg of pure product, mp 232-232.5°C; lit., mp 228-229.5°C (4), mp 227-229°C (17).

Concentration of the mother liquor gave a less pure second crop (284 g). This material was recrystallized from toluene to give an additional 225 g of pure product, mp 230.5-231.5°C.

The combined yield was 2.43 kg (95%).

^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1 H, H-7), 8.10-7.95 (m, 4 H, phthalimide), 7.55 (t, J=8.1 Hz, H-5'), 7.45 (s, 1 H, H-3), 7.42 (d, J=8.4 Hz, 1 H, H-4') 7.26 (s, 1 H, H-2'), 7.04 (d, J=8.1 Hz, 1 H, H-6'), 3.79 (s, 3 H, OCH_3), 2.63 (s, 3 H, $ArCH_3$).

Anal. Calcd for $C_{26}H_{16}ClF_3N_2O_4$ (512.87): C, 60.89; H, 3.14; Cl, 6.91; F, 11.11; N, 5.46. Found (1st crop): C, 60.97; H, 3.00; Cl, 6.98; F, 10.99; N, 5.40. Found (2nd crop): C, 60.91; H, 3.04; Cl, 6.95; F, 11.03; N, 5.43.

Thin-Layer Chromatography EM Science Silica Gel 60 F_{254}

Eluent	Rf	Comment
Toluene-methanol (4:1)	0.74	Homogeneous
Ethyl acetate	0.73	Homogeneous

Materials

Compound 5	Ash Stevens Inc., Lot No. KB-02-137
Ethylene dichloride	Vulcan, Lot Nos. 0550050293 and 055005294
Phosphorus oxychloride	Rhone-Poulenc, Lot No. 080220
Sodium hydroxide, ACS reagent	J.T. Baker, Lot No. H02937
	Spectrum Chemical Corp., Lot No. JX072
Water, deionized	Ash Stevens Inc.
Magnesium sulfate, anhydrous, technical	Chemisphere Corp., Lot No. G20420
Sodium bicarbonate, ACS reagent	Spectrum Chemical Corp., Lot No. IB155
Norit A	American Norit, Lot No.9213

Materials (Continued)

Ethanol, reagent	Aaper Alcohol, Lot No. 9213
Petroleum ether (bp 35-60°C) ACS reagent	J.T. Baker, Lot No. J06656
Toluene, reagent	Mallinckrodt, Lot No. 8608KPEZ

8-Amino-2-chloro-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (7): - A 50 L three-neck flask equipped with a temperature probe, a stirrer, an addition funnel and a reflux condenser was charged with compound 6 (1213 g, 2.36 mol) and ethanol (26.2 L). A solution of hydrazine (233 g, 7.27 mol) in ethanol (1 L) was added over a 10 min period. The mixture was brought to reflux and maintained at reflux for 90 min. The mixture was cooled to 20°C and filtered. The solid was washed with cold (5°C) ethanol (2 L) and discarded. The filtrate was concentrated (aspirator) to a viscous oil. Ethyl acetate (2.5 L) was added and the solution was washed with 20% aqueous potassium hydroxide (1.8 L). The aqueous wash was backwashed with ethyl acetate (3 x 1 L). The combined organic phase was washed with water (1.8 L) and the water wash was backwashed with ethyl acetate (2 x 1.2 L). The combined ethyl acetate layer was blanketed with nitrogen and stored over anhydrous magnesium sulfate (400 g) for further processing.

An additional 1213 g of compound 6 was treated in a similar manner to give an ethyl acetate solution of crude compound 7.

The combined ethyl acetate solution from both runs was filtered and the drying agent was washed with ethyl acetate (2 L). The filtrate was concentrated to near dryness and cyclohexane (2.6 L) was added to the residue. The resulting slurry was filtered and the solid was washed with cyclohexane (1.2 L). The damp solid was dissolved in hot, nitrogen-purged cyclohexane (19.5 L). The stirred solution was allowed to cool to room temperature overnight, then it was cooled in an ice bath to 10°C. The solid was collected by filtration, washed with cold (10°C) cyclohexane (2 L) and petroleum ether (2 L) and dried at 25°C/1 mmHg for 1.5 h to give 1.64 kg of pure product 7, mp 136-136.5°C; lit., mp 135-137°C (4), mp 133-135°C (17).

The filtrate from the cyclohexane slurry was heated to reflux and treated with Norit SA3 (18 g). The mixture was filtered through a pad of celite and the filtrate was concentrated to dryness to give 55 g of crude product. Concentration of the recrystallization mother liquors gave an additional 63 g of crude product. The combined crude product (118 g) was dissolved in hot cyclohexane and the solution was treated with Norit SA3 (5 g). The mixture was filtered through a pad of celite and the filter pad was washed with cyclohexane (150 mL). The stirred filtrate was allowed to cool to room

temperature, then it was cooled to 10°C. The solid was collected by filtration, washed with cold cyclohexane (150 mL) and petroleum ether (150 mL) and air-dried to give 108 g of purified product. This material was recrystallized once more from cyclohexane to give 100 g of pure second crop product, mp 135-135.5°C.

A total of 2.43 kg of compound 6 was processed to give 1.74 kg (96%) of pure product 7. ^{1}H NMR (DMSO-d_6) δ 7.48 (t, J=8.1 Hz, 1 H, H-5'), 7.35 (d, J=7.5 Hz, 1 H, H-4'), 7.25 (s, 1 H, H-3), 7.03 (s, 1 H, H-2'), 6.97 (d, J=8.4 Hz, 1 H, H-6'), 6.92 (s, 1 H, H-7), 6.03 (br s, 2 H, NH_2), 3.71 (s, 3 H, OCH_3), 2.49 (s, 3 H, ArCH_3).

Anal. Calcd for $C_{18}H_{14}ClF_3N_2O_2$ (382.77): C, 56.48; H, 3.69; Cl, 9.26; F, 14.89; N, 7.32. Found (1st crop): C, 56.35; H, 3.73; Cl, 9.22; F, 14.63; N, 7.17. Found (2nd crop): C, 56.52; H, 3.69; Cl, 9.29; F, 14.87; N, 7.30.

Thin-Layer Chromatography EM Science Silica Gel 60 F_{254}

Eluent	Rf	Comment
Toluene-methanol (5:1)	0.69	Homogeneous
Toluene-acetonitrile (19:1)	0.44	Homogeneous

Materials

Compound 6	Ash Stevens Inc., Lot Nos. KB-02-146B and KB-02-146C
Ethanol, reagent	Aaper Alcohol, Lot No. 95D11UB-RK
Hydrazine, anhydrous	Aldrich, Lot No. 21131EN
Ethyl acetate, ACS reagent	J.T. Baker, Lot No. J28601
Potassium hydroxide, ACS reagent	Aldrich, Lot No. 07915LG
Water, deionized	Ash Stevens Inc.
Magnesium sulfate, anhydrous, reagent	J.T. Baker, Lot No. J06187
Cyclohexane, reagent	Fisher Scientific, Lot No. 952399
	J.T. Baker, Lot Nos. H29331 and J11610
Petroleum ether (bp 35-60°C) ACS	Fisher Scientific, Lot No. 945293
Norit SA3	Norit Americas, Lot No. 2347-4
Celite	Manville, no Lot No.

8-Amino-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (8): - A 12 L three neck flask equipped with a stirrer and a temperature probe was flushed with nitrogen and charged with 1-methyl-2-pyrrolidinone (3.7 L) and dry methanol (128 g, 3.99 mol). Sodium hydride (133 g of a 60% dispersion in mineral oil, 3.32 mol) was added portionwise over a period of 30 min. The mixture was stirred at ambient temperature for 30 min, then compound 7 (694 g, 1.81 mol) was added as a solid. The mixture was warmed in a water bath and at 35°C it exothermed to 45°C. The temperature was maintained at 45 ± 2°C for 75 min at which time analysis by TLC showed the reaction to be complete. The mixture was cooled to 15°C and poured into a rapidly stirred mixture of ice (2.93 kg) and water (7.5 L). Most of the sticky solid that formed in the quench was physically removed and the aqueous phase was extracted with ether (3 x 3 L). The ether extract was added to the sticky solid. Fresh ether (2 L) was added to dissolve all of the solid and the solution was washed with water (3 x 1 L). The combined water wash was extracted with ether (2 x 400 mL) and the ether extract was washed with water (2 x 200 mL). The combined organic phase was dried over magnesium sulfate (68 g). Norit SA3 (80 g) was added and the mixture was filtered through a pad of celite. The filter pad was washed with ether (1 L). The combined filtrate was concentrated to a thick oil (aspirator, water bath) and hexanes (3.6 L) was added. The resulting mixture was concentrated to a volume of ca. 2 L, cooled in an ice bath for 2 h and filtered. The solid was washed with cold hexanes (1 L) and petroleum ether (800 mL) and air-dried to give 643 g of crude product 8.

An additional 1034 g of compound 7 was processed in the same manner and gave 964 g of crude product 8.

The combined crude product (1607 g) was dissolved in ether (9 L). The ether was removed by distillation and replaced gradually with hexanes (4.4 L). When product crystallization began, the mixture was stirred at room temperature for 1 h, then cooled in an ice bath for 1 h. The solid was collected by filtration, washed with petroleum ether (1.5 L) and dried at 25°C/1 mmHg for 2 h to give 1424 g of pure product 8, mp 116-116.5°C; lit., mp 115-116.5°C (4), mp 114-117°C (17).

All of the crystallization mother liquors were combined, treated with Norit SA3 (40 g) and magnesium sulfate (27 g), and filtered through a pad of celite. The filter pad was washed with ether (1 L). Concentration of the filtrate gave 211 g of crude second crop product. This material was dissolved in ether (1.6 L), treated with Norit SA3 (20 g) and filtered through celite. The ether was removed by distillation and replaced with hexanes (200 mL) as described above to give 134 g of pure second crop product, mp 116-116.5°C.

A total of 1.73 kg of compound 7 was processed to give 1.56 kg (91%) of pure product 8. ^{1}H NMR (DMSO-d_6) δ 7.47 (t, J=7.8 Hz, 1 H, H-5′), 7.29 (d, J=7.5 Hz, 1 H, H-4′), 6.98 (s, 1 H, H-2′), 6.97 (d, J=7.8 Ha, 1 H, H-6′) 6.84 (s, 1 H, H-7 or H-2), 6.71 (s, 1 H, H-2 or H-7), 5.80 (br d, 2 H, NH_2), 3.93 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 2.43 (s, 3 H, Ar$\underline{CH_3}$).

Anal. Calcd for $C_{19}H_{17}F_3N_2O_3$ (378.35): C, 60.32; H, 4.53; F, 15.06; N, 7.40. Found (1st crop): C, 60.37; H, 4.60; F, 15.13; N, 7.41. Found (2nd crop): C, 60.44; H, 4.56; F, 14.87; N, 7.34.

Thin-Layer Chromatography EM Silica Gel 60 F_{254}

Eluent	Rf	Comment
Toluene-methanol (5:1)	0.54	Major
	0.74	Trace
Toluene-acetone (9:1)	0.45	Major
	0.60	Trace

Materials

1-Methyl-2-pyrrolidinone, anhydrous	Aldrich, Lot No. 09447HN
Methanol, absolute ACS (distilled from magnesium prior to use)	Aaper Alcohol, Lot No. 93L08M
Sodium hydride, 60% dispersion in mineral oil	Aldrich, Lot No. 16617JN
Compound 7	Ash Stevens Inc., Lot Nos. KB-02-154 and KB-02-155D
Water, deionized	Ash Stevens Inc.
Ethyl ether, anhydrous reagent	Fisher Scientific, Lot Nos. 956096-15, 956179-15 and 956137-15
Magnesium sulfate, anhydrous reagent	J.T. Baker, Lot No. J06187
Norit SA3	Norit Americas Inc., Lot No. 2347-4
Celite	A.T. Wagner, Lot No. 3P5-142-03
Hexanes, certified ACS	Fisher Scientific, Lot No. 952514
Petroleum ether (bp 35-60°C) certified ACS	Fisher Scientific, Lot No. 945293

1,4-Dibromopentane (9): - A 12 L three-neck flask equipped with a stirrer and a reflux condenser was charged with water (3.66 L) and sulfuric acid (4.0 L). The solution was cooled to 9°C and sodium bromide (3.2 kg, 31.07 mol) was added. 2-Methyltetrahydrofuran (1.233 kg, 14.31 mol) was added over a period of one hour while the temperature rose from 9° to 20°C. The mixture was heated at reflux for two hours and allowed to cool to room temperature overnight.

A second run of the same size was carried out simultaneously.

The reaction mixture of both runs was poured together into water (24 L) with stirring. The reaction flasks were rinsed with water (6 L) and the rinse was poured into the quench. The mixture was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with methylene chloride (3 x 3.2 L). The combined organic phase was washed successively with water (3 x 3.2 L), 5% aqueous sodium bicarbonate (2 x 1.6 L) and with 10% aqueous sodium chloride (1 x 3.2 L). The organic phase was dried over anhydrous potassium carbonate (625 g). The drying agent was removed by filtration and washed with methylene chloride (900 mL). The filtrate was concentrated (aspirator and steam bath) to give crude product, 6.082 kg.

The crude product was flash distilled at 61-68°C/0.9-2 mmHg to give 5.66 kg of product (purity by GC 92.4%). The flash distilled product was fractionated through a ten plate Oldershaw bubble plate column to remove low boiling impurities. When the distillation pot showed the absence of low boilers, the fractionation column was removed and the material was distilled to yield 4.896 kg (74%) of product, bp 53-56°C/2.5 mmHg; lit., bp 73-74°C/4.5 mmHg (4), bp 98-99°C/25 mmHg (18).

Analysis by GC showed the purity to be 97% (3% OV17 on 80-100 mesh chromosorb WHP, 2.9 m x 1/8 in column).

Materials

2-Methyltetrahydrofuran	Aldrich, Lot Nos., 00419CL and 05227KM
Sodium bromide	Spectrum Chemical Corp., Lot No. HM018
	Fisher Scientific, Lot No. 916659
Sulfuric acid	Aldrich, Lot No. 08309HG
	Fisher Scientific, Lot No. 953629
Sodium bicarbonate, ACS	Aldrich, Lot No. 14731KF
Potassium carbonate, ACS	Aldrich, Lot No. 1150TF

4-Bromo-1-phthalimidopentane (10): - A 12 L three-neck flask equipped with a stirrer and a reflux condenser was charged with 1,4-dibromopentane (2.448 kg, 10.65 mol), potassium phthalimide (1.48 kg, 8 mol) and acetone (8 L). The mixture was heated at reflux for 24 hours, then it was allowed to cool to room temperature.

A second, identical scale run was carried out simultaneously.

The combined reaction mixture of both runs was filtered and the solid was washed with acetone (3 L). The filtrate and the washings were combined and the solvent was removed under reduced pressure (aspirator and steam bath). The residue was dissolved in methylene chloride (12 L), washed with aqueous 8% potassium carbonate (6 L) and water (2 x 4 L) and dried over anhydrous potassium carbonate (800 g). The drying agent was removed by filtration, washed with methylene chloride (1.6 L) and the solvent was removed from the combined filtrate under reduced pressure (aspirator, steam bath). Excess 1,4-dibromo-pentane was removed by distillation at 24-62°C/0.4 mmHg to yield 4.424 kg of crude product as a distillation residue.

The crude product (4.424 kg) was dissolved in methylene chloride (4 L) and applied onto a column of aluminum oxide (15 cm x 58 cm containing 4.5 kg of aluminum oxide). The column was eluted with methylene chloride (22 L) until the eluate, as examined by TLC, showed the absence of product. The solvent was removed under reduced pressure (aspirator, steam bath) and then at 0.4 mmHg overnight to give 4.31 kg (91%) of product 10 as a light yellow viscous oil; lit., light yellow oil (4, 19).

Thin-Layer Chromatography Polygram Sil G/UV_{254}

Eluent	Rf	Comment
Chloroform	0.48	Major
	0.14	Trace

Materials

1,4-Dibromopentane	Ash Stevens Inc., Lot No. AP-11-65
Potassium phthalimide	Aldrich, Lot No. 05311PG
Acetone, reagent	J.T. Baker, Lot No. H09602
Methylene chloride, reagent	J.T. Baker, Lot Nos. J13629 and H40634
Potassium carbonate	J.T. Baker, Lot No. H26158
Aluminum oxide (activated neutral Brockmann 1)	Aldrich, Lot No. 16304CGT

4-Iodo-1-phthalimidopentane (11): - A 12 L three-neck flask equipped with a stirrer and a reflux condenser was charged with sodium iodide (1.345 kg, 8.97 mol) and a solution of 4-bromo-1-phthalimidopentane (2.155 kg, 7.27 mol) in acetone (7.5 L). The mixture was heated at reflux for 18 h with stirring, then cooled to 10°C.

A second, identical scale reaction was carried out simultaneously.

Both reaction mixtures were filtered together and the solid was washed with acetone (3.2 L). The filtrate and the washings were combined and the solvent was removed under reduced pressure (aspirator, steam bath). The concentrate was transferred by decantation to a polyethylene tank (10 gal). The residual solid-liquid mixture was filtered and the solid was washed with methylene chloride (4 L). The filtrate was combined with the concentrate and diluted further with methylene chloride (12 L). The resultant mixture was washed successively with water (2 x 4 L), aqueous 5% sodium thiosulfate solution (2 x 4 L) and water (4 L). The organic phase was dried over anhydrous potassium carbonate (1.5 kg), treated with Norit A (164 g), and filtered through a pad of celite. The celite pad was washed with methylene chloride (3.2 L). The combined filtrate was concentrated under reduced pressure (aspirator and steam bath, then 50-55°C/0.3 mmHg for 4 h and room temperature/0.3 mmHg overnight) to give 4.024 kg of a dark colored oil. This oil (5.024 kg) was dissolved in refluxing petroleum ether (bp 50-110°C, 24 L). The solution was treated with Norit A (260 g) and filtered through celite pad. The celite pad was washed with hot petroleum ether (5 L). The filtrate was transferred to a 50 L stainless steel flask and cooled in an ice bath with stirring to below 10°C to crystallize the product. After the product crystallized, cooling was continued for 1 h and the mixture was filtered. The solid was washed with ice-cold low boiling petroleum ether (35-60°C, 4 x 1 L) and air-dried overnight. The solid was dried further at room temperature/0.3 mmHg for 4 h to give 2.734 kg (55%) of pure product 11, mp 46-47°C with prior softening at 45°C; lit. mp 45-47°C (4). ^{1}H NMR ($CDCl_3$) δ 7.85-7.77 (m, 2 H, ArH), 7.73-7.65 (m, 2 H, ArH), 4.17 (m, 1 H, C<u>H</u>I), 3.68 (t, J=6.6 Hz, 2 H, CH_2N), 1.88 (d, J=6.9 Hz, 3 H, CH_3), 1.95-1.55 (m, 4 H, CH_2).

Anal. Calcd for $C_{13}H_{14}INO_2$ (343.16): C, 45.50; H, 4.11; I, 36.98, N, 4.08. Found: C, 45.80; H, 4.09; I, 36.77; N, 4.05.

Thin-Layer Chromatography Polygram Sil G/UV_{254}

Eluent	Rf	Comment
Methylene chloride	0.44	Major
	0.03	Trace

Materials

4-Bromo-1-phthalimido-pentane	Ash Stevens Inc., Lot No. AP-11-71
Sodium iodide	J.T. Baker, Lot Nos. H45714 and H33726
Acetone, reagent	J.T. Baker, Lot No. J28650
Methylene chloride, reagent	J.T. Baker, Lot No. H40639
Potassium carbonate, anhydrous, reagent	J.T. Baker, Lot No. H26158
Petroleum ether (bp 50-110°C), reagent	J.T. Baker, Lot No. H04650
Petroleum ether (bp 35-60°C), reagent	J.T. Baker, Lot No. J10607
Sodium thiosulfate pentahydrate	J.T. Baker, Lot No. 721773
Norit A SA3	Norit America Inc., Lot No. 2347-4
Celite 545	Manville, no Lot No.

8-[(4-Phthalimido-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (12): - A 12 L three neck flask equipped with a stirrer and reflux condenser was charged with product 8 (700 g, 1.85 mol), 4-iodo-1-phthalimido-pentane (635 g, 1.85 mol), diisopropylamine (187 g, 1.85 mol) and acetonitrile (3.7 L). The mixture was heated at reflux for 24 h, then additional product 11 (635 g, 1.85 mol) and diisopropylamine (187 g, 1.85 mol) were added. The mixture was refluxed for a total of 53 h, cooled to 45°C and diluted with water (1.9 L). The mixture was stirred at room temperature overnight, then cooled in an ice bath for one hour and filtered. The solid was washed with cold (5°C) acetonitrile (500 mL), cold (5°C) isopropanol (1.25 L) and petroleum ether (1 L) and air-dried to give 898 g of crude product 12.

Crude product 12 (898 g) was dissolved in refluxing isopropanol (5 L) and the stirred solution was allowed to cool to room temperature overnight. The resulting mixture was cooled in an ice bath for one hour and filtered. The solid was washed with cold (5°C) isopropanol (1.7 L) and petroleum ether (1.4 L) and air-dried to give 869 g of once-recrystallized product 12.

Additional product 8 (744 g) was processed in a similar manner and gave 968 g of once-recrystallized product 12.

Once-recrystallized product 12 (1837 g) was dissolved in refluxing isopropanol (10 L). The stirred solution was allowed to cool to room temperature overnight, then it was cooled in an ice bath for 1 h. The solid was collected by filtration, washed with cold isopropanol (2 L) and petroleum ether (2 L) and dried at 40°C/1 mmHg for 8 h to give 1815 g of pure product 12, mp 124-126°C.

Although this product had acceptable elemental analysis, the compound was somewhat darker in color than the reference sample. Accordingly, the material was dissolved in methylene chloride (7 L). The solution was treated with Norit E Supra (240 g) and filtered through a pad of celite. The filter pad was washed with methylene chloride (1.5 L). The filtrate was concentrated under reduced pressure (steam jet, water bath) and the methylene chloride was replaced gradually with isopropanol (6 L). Concentration was continued until solid precipitated. The mixture was cooled in an ice bath and filtered. The solid was washed with cold (5°C) isopropanol (500 mL) and petroleum ether (1 L) and dried at 45°C/1 mmHg for 6 h and at 25°C/1 mmHg or 17 h to give 1.55 kg (70%) of light yellow colored product 12, mp 124-126°C; lit., mp 124-126°C (4), mp 121-124°C (17). ^{1}H NMR (DMSO-d_6) δ 7.81 (s, 4 H, phthalimide), 7.50 (t, J=8.1 Hz, 1 H, H-5'), 7.32 (d, J=7.8 Hz, 1 H, H-4'), 7.04 (s, 1 H, H-2'), 6.97 (d, J=8.1 Hz, 1 H, H-6'), 6.75 (s, 1 H, H-7 or H-2), 6.63 (s, 1 H, H-2 or H-7), 5.84 (d, J=8.8 Hz, 1 H, NH), 3.92 (s, 3 H, OCH_3), 3.78 (m, 1 H, NCH), 3.71 (s, 3 H, OCH_3), 3.63 (t, J=7.0 Hz, 3 H, NCH_2), 2.45 (s, 3 H, ArCH_3), 1.90-1.55 (m, 4 H, CH_2), 1.25 (d, J=6.4 Hz, 3 H, CHCH_3).

Anal. Calcd for $C_{32}H_{30}F_3N_3O_5$ (593.60): C, 64.75; H, 5.09; F, 9.60; N, 7.08. Found: C, 64.90; H, 5.07; F, 9.65; N, 7.05.

Thin-Layer Chromatography EM Science Silica Gel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate	0.68	Homogeneous
Toluene-acetone (19:1)	0.39	Homogeneous

Materials

Compound 8	Ash Stevens Inc., Lot Nos. KB-02-167 and KB-02-168
Compound 11	Ash Stevens Inc., Lot No. AP-11-72
Diisopropylamine 99% (distilled from calcium hydride prior to use)	Aldrich, Lot No. 00223CN
Calcium hydride	Aldrich, lot No. 08727DF
Acetonitrile, ACS reagent	J.T. Baker, Lot No. J18384
Water, deionized	Ash Stevens Inc., no Lot No.
Isopropanol, ACS reagent	J.T. Baker, Lot No. J32653
Petroleum ether (bp 35-60°C), certified ACS	Fisher Scientific, Lot No. 945293
Methylene chloride, ACS reagent	J.T. Baker, Lot No. H49624

Materials (Continued)

Norit E Supra USP 22	Norit Americas Inc., Lot No. 1070-5
Celite 545, analyzed reagent	J.T. Baker, Lot No. J21732

8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate (14) (WR 238605): - A 22 L three-neck flask, equipped with a stirrer and a reflux condenser, was charged with compound 12 (765 g, 1.29 mol), ethanol (8 L), and hydrazine (175 g, 5.46 mol). The mixture was heated at reflux and diluted with ethanol (1 L) after 1 h. After 2 h at reflux, the mixture was cooled to 15°C and filtered. The solid was washed with ethanol (1.2 L) and discarded.

A second, identical scale reaction was carried out.

The filtrates from both runs were combined and concentrated until a solid precipitated. The mixture was filtered and the solid was washed with methylene chloride (1 L) and ethanol (1 L) and discarded. The combined filtrate was concentrated further to a volume of ca. 2 L and diluted with water (1.7 L). The mixture was extracted with methylene chloride (5.2 L, 1.5 L) and the combined extract was washed successively with 25% aq. potassium hydroxide (3 x 870 mL) and water (3 x 2 L). The organic phase was dried over magnesium sulfate (176 g) and treated with Norit E Supra (230 g). The mixture was stirred for 30 min and filtered through celite (130 g). The filter pad was washed with methylene chloride (1.5 L) and the combined filtrate was concentrated at reduced pressure (steam jet, then vacuum pump, 30-40°C) to give crude product 13 in the form of a thick oil.

Crude product 13 was dissolved in warm (40°C) acetonitrile (3.5 L). A refluxing solution of succinic acid (350 g, 2.96 mol) in a mixture of methanol (700 mL) and acetonitrile (3.5 L) was added and the stirred mixture was allowed to cool to room temperature overnight. The mixture was then cooled in an ice bath for 90 min and filtered. The solid was washed with cold acetonitrile (2.3 L) and ether (2 L) and air-dried to give 1.29 kg of crude product 14, mp 147-148°C.

Crude product 14 (1.29 kg) was dissolved in refluxing isopropanol (9.6 L). The solution was allowed to cool slightly and diluted carefully with ether (2.7 L). The mixture was stirred at ambient temperature overnight, then cooled in an ice bath for 1 h and filtered. The solid was washed with cold isopropanol (2 L) and ether (2.7 L) and air-dried to give 1.25 kg of once-recrystallized product 14, mp 145.5-146°C.

Once-recrystallized product 14 (1.24 kg) was dissolved in boiling ethanol (5.3 L). The solution was filtered and the stirred filtrate was diluted carefully with ether (5.1 L). More ether was added after 20 min (2.8 L) and again after 40 min (5.1 L). The mixture was stirred at ambient temperature for 3 h, then cooled in an ice bath for 1 h. The solid was collected by filtration, washed with ethanol-ether mixture (1:2, 1.5 L) and ether (1.5 L) and air-dried overnight. The solid was dried further at 75-80°C/1 mmHg for 6 h to yield 1.075 kg (72%) of pure product 14, mp 148.5-149.5°C; lit., mp 148-150°C (4), 146-149°C (17). ^{1}H NMR (DMSO-d_6) δ 10.5-9.4 (v br s, 3 H, NH_3), 7.52 (t, J=7.9 Hz, 1 H, H-5'), 7.34 (d, J=8.1 Hz, 1 H, H-4'), 7.07 (s, 1 H, H-2'), 7.02 (dd, J=8.1, 2.3 Hz, 1 H, H-6'), 6.80 (s, 1 H, H-7 or H-2), 6.72 (s, 1 H, H-2 or H-7), 5.89 (d, J=8.2 Hz, 1 H, NH), 3.99 (s, 3 H, OCH_3), 3.9-3.8 (m, 1 H, NCH), 3.80 (s, 3 H, OCH_3), 2.88 (t, 2 H, NCH_2), 2.49 (s, 3 H, $ArCH_3$), 2.31 (s, 4 H, $COCH_2CH_2CO$) 1.85-1.60 (m, 4 H, $CH_2CH_2CH_2N$), 1.30 (d, J=6 Hz, 3 H, $CHCH_3$).

Anal. Calcd for $C_{28}H_{34}F_3N_3O_7$ (581.59): C, 57.83; H, 5.89; F, 9.80; N, 7.23. Found: C, 57.92; H, 5.95; F, 9.90; N, 7.21.

Thin-Layer Chromatography EM Silica Gel 60 F_{254}

Eluent	Rf	Comment
Chloroform-methanol-ammonium hydroxide (30:20:1)	0.46	Homogeneous
Ethanol-ammonium hydroxide (19:1)	0.36	Homogeneous
Butanol-acetic acid-water (5:3:2)	0.75	Homogeneous

Materials

Compound 12	Ash Stevens Inc., Lot No. KB-02-195
Ethanol, reagent	Aaper Alcohol, Lot No. 95J11UB-RQ
Hydrazine, anhydrous 98%	Aldrich, Lot No. 21131EN
Methylene chloride, ACS reagent	J.T. Baker, Lot No. H49624
Water, deionized	Ash Stevens Inc., no Lot No.
Potassium hydroxide, ACS reagent	Aldrich, Lot No. 07915LG
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. J06187
Norit E Supra USP 22	Norit Americas, Lot No.
Celite 545, analyzed reagent	J.T. Baker, Lot No. J21732
Acetonitrile, ACS reagent	J.T. Baker, Lot No. J18384 1070-5

Materials (Continued)

Succinic acid, ACS reagent 99%	Aldrich, Lot No. 02411KN
Methanol, ACS	Aaper Alcohol, Lot No. 93L08M
Ether, ACS reagent	Fisher Scientific, Lot Nos. 956137-15 and 956051-15
Isopropanol, ACS reagent	J.T. Baker, Lot No. J32653

4.3 3-Dimethylaminocarbonyloxypyridine (WR 256235)

A solution of dimethylcarbamyl chloride (28.3 g, 0.26 mol) in dry tetrahydrofuran (50 mL) was added dropwise over a 30 min period to a cold (0-5°C) solution of 3-hydroxypyridine (20 g, 0.21 mol) and triethylamine (21.3 g, 0.21 mol) in dry tetrahydrofuran (200 mL) maintained under a nitrogen atmosphere. After the addition was completed, the mixture was allowed to warm over a 1.5 h period to room temperature, then it was heated at reflux for 2 h. The mixture was cooled to room temperature and the triethylamine hydrochloride salt was removed by filtration. The filtrate was concentrated (35-40°C/aspirator) to a brown oil, 39.8 g. The oil was distilled and the fraction, bp 108-110°C/0.1 mmHg was collected to give purified off-white title compound, 28.6 g. Analysis by GC showed the purity to be 99.7%.

The purified product, 28.1 g, was redistilled to give pure title compound as a colorless oil, 22.7 g (65%) bp 115-118°C/0.15 mmHg; lit., bp 90°C/0.25 mmHg (6), bp 89-90°C/3.5 mmHg (7). ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J=2.7 Hz, 1 H, H-2), 8.32 (dd, J=1.5, 4.5 Hz, 1 H, H-6), 7.45-7.39 (m, 1 H, H-4), 7.20 (dd, J=4.5, 8.1 Hz, 1 H, H-5), 2.99 (s, 3 H, NCH_3), 2.89 (s, 3 H, NCH_3).

Anal. Calcd for $C_8H_{10}N_2O_2$ (166.18): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.68; H, 5.94; N, 16.64.

GC Analysis

Column: 10% Carbowax 1/8" x 6' stainless steel column (Alltech)
Injection and Detector temp: 210°C
Oven temp: 200°C
Retention time: 4.9 to 5.2 min

Thin-Layer Chromatography

Eluent	Rf	Comment
Methanol-methylene chloride (1:50)	0.28	Homogeneous

Materials

3-Hydroxypyridine	Aldrich, Lot No. PN02611KV
Dimethylcarbamyl chloride	Aldrich, Lot No. KN12824MG
Triethylamine	Aldrich, Lot No. EG06902CG
Tetrahydrofuran	Chempure, Lot No. M306KJMH

4.4 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-5-hydroxy-4-methylquinoline dihydrochloride (WR 280528)

The synthesis route to the title compound is Shown in Chart No. 3.

5-Benzyloxy-6-methoxy-4-methyl-8-nitroquinoline (2): - A stirred mixture of 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline (1) (50 g, 0.21 mol), benzyl bromide (32 mL, 0.27 mol), tetrabutylammonium hydroxide (40% aq solution, 163 g, 0.25 mol), toluene (800 mL) and water (125 mL) was heated at 70°C for 2 h. Additional benzyl bromide (8 mL, 0.07 mol) and tetrabutylammonium hydroxide (35 g, 0.05 mol) were added and heating was continued for another 3.5 h. The mixture was diluted with water (800 mL) and the layers were separated. The organic layer was washed with water (3 x 1 L), dried over magnesium sulfate, then treated with charcoal (10 g) and filtered through a pad of celite. The filter pad was washed with toluene (3 x 250 mL). The combined filtrate was concentrated to dryness (aspirator/water bath) and the dark residue was dried further at 40°C/0.1 mmHg for 30 min. The residual solid was dissolved in dichloromethane (1 L) and chromatographed over silica gel (750 g) eluting with dichloromethane (6 L). The product-containing fractions were combined and concentrated to dryness (aspirator/water bath). The solid residue was dissolved in a boiling mixture of hexanes and tetrahydrofuran (2:1, 1 L). The solution was diluted with hexanes (300 mL), allowed to cool to room temperature, then cooled in an ice bath for 90 min. The solid was collected by filtration, washed with petroleum ether (2 x 125 mL) and air-dried to give 24.1 g of purified product.

By this procedure, a total of 277 g of purified product 2 was prepared from 500 g of 5-hydroxyquinoline 1.

The purified product (277 g) was dissolved in methylene chloride (3.5 L). The solution was treated with Norit (30 g) and filtered through a pad of celite. The filter pad was washed with methylene chloride. The combined filtrate was stirred with silica gel (100 g) for 15 min, filtered, and the filter pad was washed with methylene chloride (6 x 150 mL). The filtrate was concentrated to dryness (aspirator/water bath) and the solid residue was dissolved in a boiling mixture of hexanes and tetrahydrofuran (2:1, 7.5 L). The solution was diluted with hexanes (2.5 L), stirred at room temperature overnight, then cooled in an ice bath for 2 h. The solid was collected by

filtration, washed with petroleum ether (3 x 350 mL), and air-dried to give 220 g (32%) of pure product, mp 133-135°C; lit. mp 132-134°C (8).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Hexanes-ethyl acetate (7:3)	0.52	Major
	0.00	Trace
Methylene chloride	0.13	Major
	0.00	Trace

Materials

Quinoline 1	Ash Stevens Inc., Lot No. PAS-02-156
Toluene	J.T. Baker, Lot No. G02613
Benzyl bromide, 98%	Aldrich, Lot No. 09915HF
Tetrabutylammonium hydroxide, 40% aqueous	Aldrich, Lot Nos. 0117AZ and 01719BF
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No. G10903
Norit SA3	J.T. Baker, Lot No. E4170J
Celite 545	Johns Manville, Lot No. 3AP2-195-118
Silica gel, grade 62 60-200 mesh	Davison Chemical, Lot No. 540
Methylene chloride	J.T. Baker, Lot No. G38675
Hexanes	J.T. Baker, Lot No. G38644
Tetrahydrofuran	J.T. Baker, Lot No. F34628
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot Nos. G25634 and G41622

8-Amino-5-benzyloxy-6-methoxy-4-methylquinoline (3): - A mixture of quinoline 2 (100 g, 0.308 mol), iron filings (104 g, 1.86 mol), butyl ether (260 mL), acetic acid (92 mL) and water (1 L) was heated at 86-88°C, under a nitrogen atmosphere, for 90 min. Analysis by TLC (hexanes-ethyl acetate, 7:3) showed the absence of starting material. (In order to avoid product discoloration, all subsequent manipulation were conducted under a nitrogen atmosphere.) The mixture was cooled to 50°C and filtered through a pad of celite. The reaction flask and filter pad were washed with ethyl acetate (3 x 750 mL). The layers were separated and the organic phase was washed successively with saturated aq. sodium bicarbonate (3 x 1 L) and water (3 x 1 L), then dried over magnesium sulfate. The solution was treated with Norit (100 g), heated at reflux for 30 min and filtered through a pad of celite. The filter pad was washed with ethyl acetate (350 mL) and the combined filtrate was concentrated to dryness (aspirator, water bath). The residual solid was dissolved in

tetrahydrofuran (400 mL) and the solution was diluted with hexanes (800 mL). More hexanes (400 mL) was added when the product began to crystallize. The mixture was stored at room temperature overnight, cooled in an ice bath for 30 min and filtered. The solid was washed with petroleum ether (3 x 100 mL) and air-dried to give 70 g (77%) of pure product, mp 74-76°C; lit., mp 58-60°C (8).

Additional product (72 g) mp 75-76°C was prepared in the same manner.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Hexanes-ethyl acetate (7:3)	0.22	Major
	0.00	Trace
Methylene chloride-methanol (19:1)	0.64	Major
	0.00	Trace

Materials

Compound 2	Ash Stevens Inc., Lot No. PAS-03-183
Iron filings, degreased	MC/B, Lot No. 3H17
Acetic acid, glacial	Ashland, Lot No. 011171E
Butyl ether, 99%	Aldrich, Lot No. 09126DF
Celite 545	J.T. Baker, lot No. E49707
Ethyl acetate	J.T. Baker, Lot No. G10638
Sodium bicarbonate	Fisher Scientific, Lot No. 923895
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No. G10903
Norit SA3	J.T. Baker, Lot Nos. E41700 and E08711
Tetrahydrofuran	Quaker Oats, Lot No. QL-13M5
Hexanes	J.T. Baker, Lot No. G38644
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. G41622

5-Benzyloxy-6-methoxy-4-methyl-8-phthalimidoquinoline (4): - A mixture of compound 3 (147 g, 0.499 mol), phthalic anhydride (81.4 g, 0.55 mol), and toluene (2.25 L) was heated at reflux for 2 h during which time a portion of the solvent (700 mL) was removed by distillation. The mixture was cooled to 50°C, diluted with hexanes (2.1 L) and stirred at room temperature for 1 h. The solid was collected by filtration, washed with petroleum ether (3 x 250 mL) and air-dried to give 200 g (94%) of product, mp 240-242°C; lit., mp 238-240°C (8).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Toluene-tetrahydrofuran (4:1)	0.57	Homogeneous
Methylene chloride-methanol (19:1)	0.87	Homogeneous

Materials

Compound 3	Ash Stevens Inc., Lot Nos. PAS-03-187, -194, -199 and -201
Phthalic anhydride	J.T. Baker, Lot No. F46716
Toluene	J.T. Baker, Lot No. G02613
Petroleum ether (bp 35-60°)	J.T. Baker, Lot No. G41622

5-Benzyloxy-6-methoxy-4-methyl-8-phthalimidoquinoline-1-oxide (5): - A solution of m-chloroperbenzoic acid (295 g, ca. 1.2 mol) in methylene chloride (3 L) was dried over magnesium sulfate (150 g) and filtered. The filtrate was added to a solution of compound 4 (184 g, 0.434 mol) in methylene chloride (5 L). The mixture was stirred at room temperature for 5 h, treated with 10% aq. potassium carbonate (9.2 L) and stirred for 1 h. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 1.5 L). The combined methylene chloride extract was washed with brine (2 L), dried over potassium carbonate (150 g), and treated with Darco (50 g). The mixture was filtered through celite and the filtrate was concentrated to dryness (aspirator, water bath) to give 184 g of crude product. The crude product was impregnated on silica gel (200 g) and chromatographed over silica gel (1.5 kg). The column was eluted with toluene (10 L), then with toluene-tetrahydrofuran (9:1, 35 L; 4:1, 15 L and 7:3, 45 L). The product-containing fractions were combined and concentrated to dryness. The solid residue was dissolved in boiling tetrahydrofuran (10 L). The solution was concentrated atmospherically to a volume of 7 L, allowed to cool until turbidity became evident and diluted with hexanes (7 L). The mixture was cooled in an ice bath for 2 h and filtered. The solid was washed with petroleum ether (3 x 650 mL) and air-dried to give 137 g (72%) of product, mp 238-240°C; lit., mp 237-239°C (8).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Acetone	0.89	Homogeneous
Toluene-tetrahydrofuran (4:1)	0.11	Homogeneous

Materials

Compound 4	Ash Stevens Inc., Lot No. PAS-03-207
Methylene chloride	J.T. Baker, Lot No. G38675
m-Chloroperbenzoic acid, tech grade, 70-75%	Janssen, Lot No. 63449/1
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No. G10903
Potassium carbonate, anhydrous	Johnson Mathey, Lot No. J16A15
Sodium chloride	Spectrum, Lot No. HD226
Darco KB	Aldrich, Lot No. 12411HZ
Celite 545	J.T. Baker, Lot No. F49707
Silica gel, grade 62 60-200 mesh	Davison Chemical, Lot No. 540
Tetrahydrofuran	Fisher Scientific, Lot No. 920625
Toluene	J.T. Baker, Lot No. G02613
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. G50624

5-Benzyloxy-2-chloro-6-methoxy-4-methyl-8-phthalimidoquinoline (6): - A mixture of compound 5 (127 g, 0.288 mol) and phosphorus oxychloride (418 g, 2.73 mol) in chloroform (3.18 L) was heated at reflux for 2 h. The mixture was cooled to 20°C and poured into rapidly stirred ice/water (6.2 L). The quench was basified with ammonium hydroxide (1.23 L) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 x 750 mL) and the combined organic phase was dried over magnesium sulfate (100 g) and filtered. The drying agent was washed with methylene chloride (3 x 250 mL). The combined filtrate was treated with silica gel (200 g). The mixture was stirred for 15 min and filtered. The silica gel was washed with methylene chloride (3 x 250 mL) and the combined filtrate was concentrated (aspirator, steam bath) to dryness. The solid residue (128.5 g) was dissolved in boiling tetrahydrofuran (1 L). The solution was diluted with hexanes (2 L) and cooled in an ice bath for 2 h. The solid was collected by filtration, washed with petroleum ether (3 x 150 mL) and air-dried to give 123 g of purified product. This material was recrystallized once more from a mixture of tetrahydrofuran (750 ml) and hexanes (1.5 L) and air-dried to constant weight to give 121 g (91.5%) of pure product, mp 190-192°C; lit., mp 189-191°C (8).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Toluene-tetrahydrofuran (1:1)	0.88	Homogeneous
Hexanes-ethyl acetate (7:3)	0.36	Homogeneous

Materials

Compound 5	Ash Stevens Inc., Lot No. PAS-03-229
Chloroform	J.T. Baker, Lot No. G38675
Methylene chloride	Vulcan, Lot No. 1531062393
Phosphorus oxychloride, 99%	Aldrich, Lot No. 04003MV
Ammonium hydroxide	J.T. Baker, Lot No. F43050
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No. G10903
Silica gel, grade 62, 60-200 mesh	Davison Chemical, Lot No. 540
Tetrahydrofuran	Quaker Oats, Lot No. 0L13M5
Hexanes	J.T. Baker, Lot No. G38644
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. G50624

8-Amino-5-benzyloxy-2-chloro-6-methoxy-4-methylquinoline (7): - A mixture of compound 6 (108.5 g, 0.236 mol), anhydrous hydrazine (113 g, 3.53 mol), and ethanol (2.7 L) was heated at reflux for 1 h. The mixture was cooled to 20°C, filtered, and the solid was washed with ethanol (3 x 350 mL). The combined filtrate was concentrated (aspirator, water bath) to a red oil which was redissolved in ethyl acetate (1.5 L). The solution was filtered to remove some insolubles and the solid was washed with ethyl acetate (3 x 150 mL). The combined filtrate was washed with 20% aq. potassium hydroxide (3 x 700 mL) and the wash was backwashed with ethyl acetate (4 x 500 mL). The ethyl acetate solution was dried over magnesium sulfate (75 g), treated with Norit (80 g) and heated at reflux for 30 min. The mixture was filtered through a pad of celite and the filter pad was washed with ethyl acetate (3 x 350 mL). The filtrate was concentrated to dryness (aspirator, water bath) to give 78.2 g of crude product. The crude solid product was dissolved in boiling isopropanol (1.5 L) and the stirred solution was diluted at 5 min intervals with water (3 x 750 mL). The stirred mixture was blanketed with nitrogen and cooled in an ice bath for 45 min. The solid was collected by filtration, washed with cold (0°C) petroleum ether (3 x 350 mL) and dried at 50°C/15 mmHg for 17 h to give 63.5 g (82%) of product, mp 97-99°C; lit., mp 98-100°C (8).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Toluene-tetrahydrofuran (1:1)	0.82	Homogeneous
Hexanes-ethyl acetate (7:3)	0.28	Homogeneous

Materials

Compound 6	Ash Stevens Inc., Lot No. PAS-03-240
Ethanol, anhydrous	Aaper Alcohol, Lot No. 9SH034A-R
Hydrazine, anhydrous	Aldrich, Lot Nos. 01427KX and 07326MF
Ethyl acetate	J.T. Baker, Lot No. G10638
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No.
Norit SA3	J.T. Baker, Lot No. E41700
Celite 545	J.T. Baker, Lot No. F49707
Isopropanol	Spectrum Chemical Corp., Lot No. HU026
Potassium hydroxide	Aldrich, Lot No. 03102KX
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. G50624

8-Amino-5-benzyloxy-2,6-dimethoxy-4-methylquinoline (8): - Sodium metal (16.8 g, 0.73 mol) was added portionwise to dry methanol (335 mL). After the metal had reacted, the solution was concentrated under reduced pressure to a thick oil. A solution of compound 7 (61.5 g, 0.187 mol) in 1-methyl-2-pyrrolidinone (550 mL) was added to the oil and the mixture was heated at 50-55°C for 2.5 h. The mixture was cooled to 20°C, poured into saturated sodium chloride solution (2.5 L) and the aqueous quench was extracted with ethyl acetate (1 x 750 mL, 4 x 350 mL). The combined extract was dried over magnesium sulfate, filtered, and the filtrate was concentrated (aspirator, water bath) to a brown oil. The oil was dissolved in ether (1.5 L) and the solution was washed with water (4 x 500 mL). The ether solution was dried over magnesium sulfate, treated with Norit (20 g), and heated at reflux for 20 min. The mixture was filtered through a pad of celite and the filter pad was washed with ether (3 x 250 mL). The combined filtrate was concentrated to dryness to give a brown solid (72 g). The solid was dissolved in a mixture of hexanes-ethyl acetate (7:3, 600 mL) and chromatographed over silica gel (1.2 kg). The column was eluted with hexanes-ethyl acetate (4:1, 20 L). The product-containing fractions were combined and concentrated (aspirator-water bath) to give 52 g of crude product. The crude product (52 g) was dissolved in boiling cyclohexane (800 mL). The stirred solution was allowed to cool slowly until the product began to crystallize, then it was cooled in an ice bath to 8°C. The solid was collected by filtration, washed with cold (5°C) petroleum ether, and air dried to constant weight to give 48.6 g (80%) of pure product, mp 90.5-92°C; lit., mp 91-92°C (8).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Toluene-tetrahydrofuran (1:1)	0.75	Homogeneous
Hexanes-ethyl acetate (7:3)	0.40	Homogeneous

Materials

Compound 7	Ash Stevens Inc., Lot No. PAS-03-252
Methanol, reagent	Fisher Scientific, Lot No. 911038
Sodium metal	Aldrich, Lot No. 06717LZ
1-Methyl-2-pyrrolidinone	Aldrich, Lot No. 01716MY
Ethyl acetate	J.T. Baker, Lot No. H06607
Sodium chloride	Spectrum Chemical Corp., Lot No. HD226
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No. G10638
Norit SA3	J.T. Baker, Lot No. E08711
Celite 545	J.T. Baker, Lot No. F49707
Silica gel, grade 62, 60-200 mesh	Davison Chemical, Lot No. 540
Ether, anhydrous	Fisher Scientific, Lot No. 931431-15
Hexanes	J.T. Baker, Lot No. G38644
Cyclohexane	Fisher Scientific, Lot No. 933554
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. G50624
Water, deionized	Ash Stevens Inc., no Lot No.

5-Benzyloxy-2,6-dimethoxy-4-methyl-8-[(1-methyl-4-phthalimidobutyl)amino]quinoline (9): - A mixture of compound 8 (18.0 g, 0.055 mol), 4-iodo-1-phthalimidopentane (28.8 g, 0.084 mol), powdered potassium carbonate (16.2 g, 0.12 mol), and 1-methyl-2-pyrrolidinone (360 mL) was heated at 45-48°C for 17 h. More 4-iodo-1-phthalimidopentane (10.8 g, 0.032 mol) and powdered potassium carbonate (6.3 g, 0.046 mol) were added and the heating was continued for a total of 45 h. The mixture was cooled to 30°C, treated successively with water (360 mL), 20% aq. sodium bisulfite (75 mL), and 20% aq. potassium carbonate (100 mL) and extracted with ether (8 x 150 mL). The combined ether extract was washed with water (5 x 500 mL), dried over magnesium sulfate, and treated with Norit. The mixture was filtered through a pad of celite and the filter pad was washed with ether (3 x 75 mL). The combined filtrate was concentrated (aspirator, water bath) to a red oil. The oil was impregnated on silica gel (50 g) and chromatographed over silica gel (Davison, 650 g). The column was eluted with hexanes (4 L), then with tetrahydrofuran-hexanes (1,2,3 and 4% THF, 2 L each; 4.5 and 5% THF, 4 L each; 6 and 7%

THF, 2 L each; 8 and 9% THF, 1 L each). The product-containing fractions were combined and concentrated to a red oil. The oil (25.9 g) was dissolved in boiling ethanol (1.6 L). The stirred solution was allowed to cool to room temperature overnight, then it was cooled in an ice-bath for 1 h. The solid was collected by filtration, washed with cold (0°C) ethanol (2 x 50 mL) and petroleum ether (2 x 75 g) and air-dried to give 19.7 g of partially purified product. This material was combined with 21.3 g of similar quality product and dissolved in boiling hexanes (3.5 L). The solution was allowed to cool to room temperature and filtered. The solid was dried at 60°C/15 mmHg for 2 h to give 39 g of product, mp 83-85°C. Analysis by TLC showed the presence of a polar impurity. Accordingly, the compound was purified further as follows.

The partially purified product (15 g) was dissolved in a minimum volume of methylene chloride and chromatographed over silica gel (EM, 200 g). The column was eluted with a mixture of toluene and freshly distilled ethyl ether (4:1). The product-containing fractions were combined, treated with charcoal (3 g) and filtered through a celite pad. The filtrate was concentrated (aspirator) to an amber oil. The oil was dissolved in warm ethanol (300 mL) and the solution was diluted with isopropanol (150 mL). The clear solution was stirred at room temperature overnight, then refrigerated for 5 h. The resulting mixture was filtered and the solid was dried at 25°C/0.5 mmHg to give 13 g (87% recovery) of pure product as yellow crystals, mp 91-93°C.

An additional 14.5 g of partially purified compound was processed in a similar manner to give 12.5 g of pure product, mp 91-93°C. ^{1}H NMR ($CDCl_3$) δ 7.79 (m, 2 H), 7.67 (m, 2 H), 7.50 (m, 2 H), 7.42-7.28 (m, 3 H), 6.61 (d, J=0.9 Hz, 1 H), 6.49 (s, 1 H), 5.63 (d, J=8.3 Hz, 1 H), 4.94 (s, 2 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.74 (m, 2 H), 3.65 (m, 1 H), 2.73 (s, 3 H), 2.00-1.60 (m, 4 H), 1.29 (d, J=6.1 Hz, 3 H).

Anal. Calcd for $C_{32}H_{33}N_3O_5$ (539.61): C, 71.22; H, 6.16; N, 7.79. Found: C, 71.26; H, 6.24; N, 7.82.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Toluene-ether (4:1)	0.64	Homogeneous

Materials

Compound 8	Ash Stevens Inc., Lot No. PAS-03-267
4-Iodo-1-phthalimidopentane	Ash Stevens Inc., Lot No. PAS-02-178
1-Methyl-2-pyrrolidinone	Aldrich, Lot No. 03406DG
Potassium carbonate, anhydrous	Fisher Scientific, Lot No. 935822
Magnesium sulfate, anhydrous	Chemisphere Corp., Lot No. G10903
Sodium bisulfite	Fisher Scientific, Lot No. 944187
Silica gel, grade 62	Davison Chemical, Lot No. 540
Hexanes	J.T. Baker, Lot No. H14624
Tetrahydrofuran	J.T. Baker, Lot No. F34628
Ethanol, reagent	Aaper Alcohol, Lot No. 93L14 VWR Scientific, Lot No. 950412
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. G50624
Norit SA3	J.T. Baker, Lot No. G49725
Methylene chloride	J.T. Baker, Lot No. H40639
Toluene	J.T. Baker, Lot No. H15630
Ethyl ether	Fisher Scientific, Lot No. 956050-15 and 943933-15
Isopropanol	Chempure, Lot No. M158KPHA
Silica gel	EM Science, Lot No. 3007201
Charcoal, decolorizing	Fluka, Lot No. 301730-1-891

8-[(4-Amino-1-methylbutyl)amino]-5-benzyloxy-2,6-dimethoxy-4-methylquinoline dihydrochloride (10): - A mixture of compound 9 (10 g, 18.5 mmol), ethanol (200 mL), and anhydrous hydrazine (2.38 g, 74.3 mmol) was heated at reflux for 2.5 h. The mixture was cooled to room temperature, then it was cooled in an ice bath for 20 min and filtered under argon. The solid was washed with ethanol (20 mL) and discarded. The filtrate was evaporated (oil pump) to near dryness and the residue was dissolved in methylene chloride (40 mL). The solution was washed with 25% aq. potassium hydroxide (1 x 4 mL), water (1 x 40 ml), dried (K_2CO_3), and filtered. The filtrate was concentrated (oil pump) to a gum, and the gum was dissolved in ethanol (40 mL). The solution was cooled in an ice bath and treated with ethanolic hydrogen chloride (10 N, 3 mL). The solvent was removed at reduced pressure (aspirator) to give a dark green foam. The foam was dissolved in methanol (30 ml). The solution was treated with charcoal (1.4 g), filtered through a celite pad, and the filter pad was washed with methanol (10 mL). The combined filtrate was concentrated (aspirator) to dryness and the residual solid was dissolved in warm ethanol (30 mL). The solution was stirred at room temperature for 2 h, cooled in an ice-bath for 2 h, and

refrigerated overnight. The solid was collected by filtration and dried at 25°C/0.7 mmHg to give 4.46 g (50%) of product mp 171.5-173°C (dec).

An additional 19.4 g of compound 9 was processed in this manner and gave 7.87 g of product.

The combined product (12.33 g) was dissolved in boiling ethanol (130 mL). The solution was seeded with product 10 and stirred at room temperature for 2 h and in an ice-bath for 4 h. The solid was collected by suction filtration, washed with a mixture of isopropanol and hexane (1:1, 25 mL), and dried at room temperature/1 mmHg for 5 h to give 9.5 g (77% recovery) of pure product as light tan crystals, mp 173-175°C (dec). The analytical sample was dried further at 60°C/1.0 mmHg for 2 h. ^{1}H NMR (DMSO-d_6) δ 8.19 (br s, 3 H, D_2O exchangeable), 7.80 (br s, 1 H, H-7), 7.54-7.46 (m, 2 H, ArH), 7.46-7.32 (m, 3 H ArH), 6.86 (s, 1 H, H-3), 5.08 (s, 2 H, Ar$\underline{CH_2}$), 4.03 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 3.90 (m, 1 H, NCH), 2.77 (m, 2 H, $\underline{CH_2}N$), 2.71 (s, 3 H, Q-CH_3), 2.00-1.60 (m, 4 H, CH_2), 1.32 (d, J=6.8 Hz, 3 H, CH$\underline{CH_3}$).

Anal. Calcd for $C_{24}H_{31}N_3O_3 \cdot 2$ HCl (482.46): C, 59.75; H, 6.89; Cl, 14.70; N, 8.71. Found: C, 59.62; H, 6.80; Cl, 14.47; N, 8.80.

Thin-Layer Chromatography Analtech HPTLC-RPSF

Eluent	Rf	Comment
Methanol-0.2 M NaH_2PO_4 (4:1)	0.47	Homogeneous

Materials

Compound 9	Ash Stevens Inc., Lot Nos. CT-6-297 and CT-6-298
Hydrazine, anhydrous	Aldrich, Lot No. 07326MF
Ethanol	VWR Scientific, Lot No. 9504125
Methanol	Mallinckrodt, Lot No. 3016KPEP
Methylene chloride	J.T. Baker, Lot No. H40639
Potassium hydroxide	Sigma Chemical, Lot No. 35H0249
Potassium carbonate	Fluka, Lot No. 333630-1-994
Charcoal	Fluka, Lot No. 301730-1-891
Celite	Celite Corp., Lot No. 307

8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-5-hydroxy-4-methylquinoline dihydrochloride (WR 280528)(11): - For this preparation, all solvents were deoxygenated prior to use. Product isolation and purification was conducted under argon atmosphere.

A solution of compound 10 (1 g, 2.07 mmol) in ethanol (25 mL) containing water (0.25 mL) was hydrogenated (50 psi) for 1 h over palladium black catalyst (100 mg). The reaction mixture was filtered under argon. The filtrate was treated with ethanolic hydrogen chloride (10 N, 1 drop) and evaporated (oil pump) to dryness. The residual solid was dissolved in hot ethanol (4 mL). After cooling to room temperature, the stirred solution was seeded with a few crystals of the product isolated from a probe reaction. When the solution became turbid, petroleum ether (2 mL) was added. The mixture was stirred at room temperature for 30 min and in an ice-bath for 30 min, then refrigerated overnight. The solid was collected by filtration and dried at 25°C/0.7 mmHg to give 0.6 g (74%) of product as off-white crystals, mp 166-168°C (dec).

In this manner, an additional 8.4 g of compound 10 was processed in two runs to give 5.3 g of product.

The combined product (5.9 g) was dissolved in hot ethanol (35 mL) and the solution was filtered. The cool filtrate was seeded with a few crystals of the product and diluted with petroleum ether (20 mL). The mixture was stirred for 2 h with ice-cooling, then refrigerated over the weekend. The product was collected by suction filtration, washed with a cold mixture of ethanol (5 mL) and petroleum ether (10 mL), and dried at 25°C/0.7 mmHg to give 4.2 g (55%) of pure target compound as off-white crystals, mp 167-169°C (dec). ^{1}H NMR (DMSO-d_6) δ 11.08 (br s, 2 H, D_2O exchangeable), 9.70 (br s, 1 H, D_2O exchangeable), 8.23 (s, 3 H, D_2O exchangeable), 7.96 (s, 1 H, H-7), 6.79 (s, 1 H, H-3), 4.04 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.88 (m, 1 H, NCH), 2.81 (s, 3 H, ArCH_3), 2.77 (m, 2 H, CH_2N), 2.00-1.60 (m, 4 H, CH_2), 1.32 (d, J=6.4 Hz, 3 H, $CHCH_3$).

Anal. Calcd for $C_{17}H_{25}N_3O_3 \cdot 2$ HCl (392.34): C, 52.04; H, 6.94; Cl, 18.07; N, 10.71. Found: C, 51.88; H, 6.83; Cl, 18.27; N, 10.63.

Thin-Layer Chromatography Kodak Chromgram 13254 Cellulose

Eluent	Rf	Comment
Methanol-toluene (2:3)	0.87	Homogeneous

Materials

Compound 10	Ash Stevens Inc., Lot No. CT-7-14
Palladium black	Aldrich, Lot No. BZ06115BY
Ethanol, anhydrous	VWR Scientific, Lot No. 9504125
Petroleum ether (bp 35-60°C)	EM Science, Lot No. 31133135

4.5 3-Methylaminocarbonyloxypyridine (WR 178197)

Methyl isocyanate (16 mL, 15.47 g, 0.27 mol) was added to 3-hydroxypyridine (10 g, 0.105 mol) and the mixture was stirred at room temperature in a tightly stoppered flask for 20 h. (A solution formed within 5-10 min). The excess methyl isocyanate was removed under reduced pressure (35-45°C/aspirator pressure for 30 min, then 25°C/0.1 mmHg for 3.5 h) to give 15.8 g (99%) of the title compound in the form of a beige colored oil. The oil solidified when refrigerated but the solid melted at room temperature. ^{1}H NMR ($CDCl_3$) δ 8.37 (d, J=2.4 Hz, 1 H, H-2), 8.34 (dd, J=1.2, 4.8 Hz, 1 H, H-6), 7.50-7.42 (m, 1 H, H-4), 7.22 (dd, J=4.8, 8.4 Hz, 1 H, H-5), 6.20 (br s, 1 H, NH), 2.76 (d, J=4.8 Hz, 3 H, NCH_3).

Anal. Calcd for $C_7H_8N_2O_2$ (152.15): C, 55.26; H, 5.30; N, 18.41. Found: C, 55.06; H, 5.37; N, 18.71.

Thin-Layer Chromatography: Analtech Silica Gel GF

Eluent	Rf	Comment
Methanol-methylene chloride (1:20)	0.38 0.24, 0.47, 0.00	Major Trace impurities
Acetonitrile-ethyl acetate (1:4)	0.37 0.20, 0.00	Major Trace impurities

Materials

3-Hydroxypyridine (recrystallized prior to use)	Aldrich, Lot No. PN02611KV
Methyl isocyanate	Aldrich, Lot No. PN07101HN

4.6 1-Methyl-3-methylaminocarbonyloxypyridine iodide (WR 280593)

Methyl isocyanate (7.5 mL, 7.25 g, 0.13 mol) was added to 3-hydroxypyridine (4.1 g, 0.043 mol) and the mixture was stirred at room temperature in a tightly stoppered flask for 20 h. The excess methyl isocyanate was removed under reduced pressure (24°C/aspirator pressure, then 35-40°C/0.1 mmHg for 45 min) to give an oil.

A solution of this oil and iodomethane (11.15 g, 0.078 mol) in dry tetrahydrofuran (40 mL) was stirred at room temperature for 19 h. The light yellow solid was collected by filtration, washed with dry tetrahydrofuran (2 x 10 mL) and petroleum ether (25 mL) and dried at 25°C/0.1 mmHg for 1 h to give 11.16 g (88%) of the title compound.

A portion of this material (3.53 g) was dissolved in acetonitrile (17.5 mL) at 37-39°C. The solution was filtered (gravity) and the filtrate was diluted portionwise with ethyl acetate (10 mL and 7.5 mL). The mixture was stirred for 15 min and filtered. The light yellow solid was washed with dry tetrahydrofuran (2 x 10 mL) and petroleum ether (25 mL) and dried at 25°C/0.25 mmHg for 4 h to give pure product, 2.65 g (75% recovery), mp 118-120°C. ^{1}H NMR (CD_3CN) δ 8.87 (s, 1 H, H-2), δ 8.73 (d, J=6 Hz, 1 H, H-6), 8.42 (dd, J=1.5, 8.7 Hz, 1 H, H-4) 8.13 (dd, J=6, 8.4 Hz, 1 H, H-5), 6.71 (brs, 1 H, NH), 4.45 (s, 3 H, N^+-CH_3), 2.88 (d, J=4.8 Hz, 3 H, $NHCH_3$).

Anal. Calcd for $C_8H_{11}IN_2O_2$ (294.09): C, 32.67; H, 3.77; N, 9.53. Found: C, 32.71; H, 3.94; N, 9.66.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Methylene chloride-methanol-ammonium hydroxide (83:15:2)	0.19	Homogeneous
Methylene chloride-methanol-ammonium hydroxide (73:25:2)	0.39 0.26	Trace Major

Materials

3-Hydroxypyridine, purified	Ash Stevens Inc., Lot No. DJD-14-189
Methyl isocyanate	Aldrich, Lot No. KV01117EL
Tetrahydrofuran (distilled from LAH prior to use)	Chempure, Lot No. M306KJMH
Iodomethane	Aldrich, Lot No. KG11212JG

Materials (Continued)

Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. H05616
Acetonitrile	Burdick and Jackson, Lot No. BF350
Ethyl acetate	Fisher Scientific, Lot No. 952646

4.7 3-Dimethylaminocarbonyloxypyridine 1-oxide (WR 280594)

A solution of commercial 3-chloroperoxybenzoic acid (ca. 70% purity, 17.1 g, 0.069 mol) in methylene chloride (350 mL) was dried over magnesium sulfate (17 g) and filtered. The filtrate was added to a solution of 3-dimethylaminocarbonyloxypyridine (7.95 g, 0.048 mol) in methylene chloride (50 mL) and the mixture was stirred at room temperature for 20 h. Aqueous potassium carbonate (28.4%, 50 mL, 0.1 mol) was added and the mixture was stirred for 15 min. The layers were separated and the aqueous layer was saved for later (see below). The organic layer was dried ($MgSO_4$), filtered through a pad of celite, and concentrated to dryness (25-30°C/aspirator). The residue (6.2 g) was dissolved in methylene chloride (20 mL) and chromatographed over silica gel (50 g, 3.7 x 9 cm). The column was washed with methylene chloride (150 mL) and 1% methanol-methylene chloride to remove impurities and impure product (2.6 g). Further elution with 5% methanol-methylene chloride (100 mL) and 10% methanol-methylene chloride (100 mL) gave pure product-containing fractions which were combined and saved. The impure product (2.6 g) was rechromatographed over silica gel (25 g, 2 x 17 cm) eluting as above. The product-containing fractions from both chromatographies were combined and concentrated to dryness (25-30°C/aspirator) to give 4.25 g of purified product.

The basic aqueous layer (see above) was concentrated to dryness (45-50°C/aspirator) and the residue was extracted with methylene chloride (200 mL, 150 mL). The combined extract was dried ($MgSO_4$), filtered, and concentrated to dryness (25-30°C/aspirator) to give additional crude product, 4 g. This material was chromatographed over silica gel (25 g, 2 x 17 cm) as above to give 3.4 g of purified product.

The combined purified product (7.65 g) was dissolved in hot toluene (40 mL, steam bath). The solution was treated with charcoal (0.75 g) and filtered through a pad of celite. The hot filtrate was refiltered (filter paper, gravity), diluted with hexanes (40 mL), and stirred at room temperature for 1 h. The beige solid was collected by filtration and dried at 25°C/0.1 mmHg for 20 h to give 6.56 g (75%) of pure title compound, mp 97-99°C. ^1H NMR ($CDCl_3$) δ 8.09 (app t, J=1.8 Hz, 1 H, H-2), 8.01 (ddd, J=1.2, 1.5, 6.0 Hz, 1 H, H-6), 7.20 (dd, J=6.3, 8.4 Hz, 1 H, H-5), 7.12 (ddd, J=1.2, 1.5, 8.4 Hz, 1 H, H-4), 3.04 (s, 3 H, NCH_3), 2.96 (s, 3 H, NCH_3).

Anal. Calcd for $C_8H_{10}NCH_3$ (182.18): C, 52.74; H, 5.53; N, 15.33. Found: C, 52.65; H, 5.45; N, 15.22.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Methylene chloride-methanol (20:1)	0.52	Trace
	0.39	Major
	0.06	Trace

Materials

2-Dimethylaminocarbonyloxy-pyridine	Ash Stevens Inc., Lot No. DJD-14-181
3-Chloroperoxybenzoic acid (70%)	Janssen Chimica, Lot No. 67045/1
Methylene chloride	J.T. Baker, Lot No. H40639
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Potassium carbonate, anhydrous	J.T. Baker, Lot No. D49104
Silica gel	EM Science, Lot No. TA572034418
Methanol	Mallinckrodt, Lot No. 3016KTBK
Toluene	J.T. Baker, Lot No. J30661
Hexanes	Fisher Scientific, Lot No. 952582
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Celite, analytical	Celite Corp., no Lot No.

4.8 8-[(4-Amino-1-methylbutyl)amino]-5-hydroxy-6-methoxy-4-methylquinoline dihydrobromide (WR 280612)

The synthesis sequence to the title compound is shown in Chart No. 4. The preparation of intermediates 2 and 3 was described in section 4.4.

5-Benzyloxy-6-methoxy-4-methyl-8-[(1-methyl-4-phthalimidobutyl)amino]quinoline (4): - A mixture of 8-aminoquinoline 3 (31.6 g, 0.107 mol), 4-iodopentylphthalimide (55.65 g, 0.162 mol), finely powdered anhydrous potassium carbonate (60.14 g, 0.435 mol) and 1-methyl-2-pyrrolidinone (300 mL) was heated at 47-48°C for 50 h. Additional 4-iodopentylphthalimide was added during the reaction period at 4.5 h (20.56 g, 0.06 mol), again at 21.5 h (23.51 g, 0.068 mol) and 29 h (20.32 g, 0.06 mol plus potassium carbonate, 7.37 g, 0.053 mol), and finally at 35 h (7.27 g, 0.02 mol). After 50 h, the mixture was cooled to room temperature and poured into saturated aq. sodium chloride (1.5 L). The mixture was extracted with ethyl acetate (1.5 L) and the extract was washed with water (2 x 1 L). The water wash was backwashed with ethyl acetate (500 mL). The combined organic layer was washed with aqueous sodium chloride solution (500 mL), dried ($MgSO_4$) and treated with charcoal (6 g). The mixture was

filtered through a pad of celite and the filtrate was concentrated at reduced pressure (45-50°C/aspirator) to a thick oil, 125.71 g. The oil was dissolved in ethyl acetate-hexanes (23:77, 425 mL) and chromatographed over silica gel (1 kg, 9 x 37 cm). The column was washed with ethyl acetate-hexanes (12.5:87.5, 2 L; 17.5:82.5, 2 L; 1:4, 1 L) to remove impurities. Further elution with ethyl acetate-hexanes (1:3, 1.5 L) removed impure product, 20.66 g, and continued elution (1:3, 1 L and 1:2, 2 L) gave pure product-containing fractions which were saved.

The impure product (20.6 g) was rechromatographed over silica gel (200 g, 5.8 x 19 cm) to give additional product-containing fractions. All of the product-containing fractions were combined and concentrated (40-45°C/aspirator) to give 48.8 g (89%) of the title compound in the form of a dark, orange-red oil. This material was used as such in the next step.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Ethyl acetate-hexane (1:3)	0.38	Major
	0.00	Trace

Materials

Compound 3	Ash Stevens Inc., Lot No. DJD-14-123
4-Iodopentylphthalimide	Ash Stevens Inc., Lot No. DAG-05-165
1-Methyl-2-pyrrolidinone	Aldrich, Lot No. MG08274MG
Potassium carbonate, anhydrous	Chempure, Lot No. M228KJXS
Ethyl acetate	J.T. Baker, Lot No. H29601
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Silica gel	EM Science, Lot No. TA572034418
Hexanes	Fisher Scientific, Lot No. 945237

8-[(4-Amino-1-methylbutyl)amino]-5-benzyloxy-6-methoxy-4-methylquinoline dihydrochloride (5a): - A mixture of compound 4 (28 g, 54.9 mmol), anhydrous hydrazine (6.72 g, 209 mmol), and ethanol (45 mL) was heated at reflux for 2 h under a nitrogen blanket. The reaction mixture was cooled to room temperature, then in an ice-bath for 20 min and filtered under nitrogen. The dark, reddish-brown filtrate was concentrated under reduced pressure (aspirator) and the residue was dissolved in methylene chloride (300 mL). The solution was washed rapidly with 25% aq. potassium hydroxide (1 x 180 mL), water (1 x 180 mL), and dried over potassium carbonate. The solvent was removed under reduced pressure (aspirator), and the residue (16.2 g, 42.7 mmol) was dissolved in ethanol (60 mL). The solution was treated with 10 N

ethanolic hydrogen chloride (8.4 mL) with ice-cooling. The resultant solution was concentrated (aspirator) and the residue was dissolved in warm ethanol (30 mL). To the stirred solution was added isopropanol (40 mL). The mixture was stirred at room temperature for 30 min, then cooled in an ice-bath for 3 h. The product was collected by suction filtration and dried at room temperature/0.7 mmHg for 4 h to yield 14.5 g (58%) of compound 5a as reddish brown crystals, mp 162-164°C (dec).

Materials

Compound 4	Ash Stevens Inc., Lot No. DJD-14-130
Ethanol	VWR Scientific, Lot No. 9404125
Methylene chloride	J.T. Baker, Lot No. H40639
Hydrazine, anhydrous	Aldrich, Lot No. 07426MF
Isopropanol	Chempure, Lot No. M158KPHA
Potassium hydroxide	Sigma Chemical, Lot No. 35H0249
Potassium carbonate, anhydrous	Fluka, Lot No. 333630-1-994

8-[(4-Amino-1-methylbutyl)amino]-5-benzyloxy-6-methoxy-4-methylquinoline dihydrobromide (5b): - A solution of compound 5a (14.2 g, 31.4 mmol) in methanol (30 mL) was passed through a Dowex 2 base-form resin column (ca. 370 mL, 444 meq) and the column was washed with methanol. As the product eluted from the column, 47% aq. HBr solution (14.8 g, 86.2 mmol) was added dropwise simultaneously to the eluate. The solution was concentrated to near dryness (aspirator) and the residue was dissolved in a mixture of ethanol and toluene (1:1, 30 mL). The solution was concentrated to near dryness again. This operation was repeated once more to give a brick colored solid (18.1 g). The solid was dissolved in hot ethanol (180 mL) and the solution was filtered. The reddish brown filtrate was stirred at room temperature. When the product began to crystallize, isopropanol (180 mL) was added slowly. The mixture was stirred at room temperature for 30 min and in an ice-bath for 4 h. The solid was collected by suction filtration and dried at room temperature under vacuum (0.5 mmHg) overnight to give 12.4 g (73%) of pure product as brick red crystals, mp 174-175°C (dec). ^{1}H NMR (DMSO-d_6) δ 8.58 (d, J=4.5 Hz, 1 H, QH-2) 7.79 (br s, 5 H, D_2O exchangeable), 7.55-7.49 (m, 2 H, ArH), 7.44-7.32 (m, 4 H, ArH, QH-3), 7.09 (br, s, 1 H, QH-7), 4.99 (s, 2 H, OCH_2), 4.02 (s, 3 H, OCH_3) 3.88 (m, 1 H, NCH), 2.85 (br s, 5 H, QCH_3, NCH_2), 1.80-1.61 (m, 4 H, CH_2CH_2), 1.28 (d, J=6 Hz, 3 H, $CHCH_3$).

Anal. Calcd for $C_{23}H_{29}N_3O_2 \cdot 2HBr$ (541.35): C, 51.03; H, 5.77; Br, 29.52; N, 7.76. Found: C, 50.87; H, 5.91; Br, 29.63; N, 7.72.

Thin-Layer Chromatography Analtech HPTLC-RPSF

Eluent	Rf	Comment
Methanol-0.2 M NaH_2PO_4 (4:1)	0.48	Major
	0.90	Trace

Materials

Compound 5a	Ash Stevens Inc., Lot No. CT-7-47
Methanol	Mallinckrodt, Lot No. 3016KPEP
Dowex 2-X8	BioRad, Lot No. 114081C
Ethanol	Aaper Alcohol, Lot No. 0295R
Toluene	J.T. Baker, Lot No. J30661
47% aq. HBr	J.T. Baker, Lot No. C15335
Isopropanol	Chempure, Lot No. M158KPHA

8-[(4-Amino-1-methylbutyl)amino]-5-hydroxy-6-methoxy-4-methylquinoline dihydrobromide (WR 280612)(6): - All solvents used for following process were deoxygenated. At room temperature, compound 5b (4 g, 7.39 mmol) was hydrogenated (50 psi) for 1 h over palladium black catalyst (400 mg) in methanol (40 mL). The reaction mixture was filtered under argon atmosphere and the filtrate was concentrated (oil pump) to a purple foam. In the same manner, another lot of compound 5b (8.3 g, 15.33 mmol) was processed. The combined hydrogenated product was dissolved in ethanol (30 mL) with occasional heating. The solution was filtered under argon and the homogeneous filtrate was seeded with authentic sample prepared in a probe reaction. With stirring at room temperature, petroleum ether (15 mL) was added slowly to the solution. The mixture was stirred at room temperature for 1 h and stored in the refrigerator overnight. A cold mixture of isopropanol and petroleum ether (1:1, 30 mL) was added to the mixture to make it more filterable. The product was collected by suction filtration under argon blanket and dried at room temperature under reduced pressure (0.5 mmHg) for 8 h to give 9.3 g (90%) of pure target compound as orange-brown crystals. ^1H NMR showed that the compound contained ca. 0.4% of ethanol (by weight). The compound was dried further at 70°C/0.3 mmHg for 4 h. The NMR spectrum of the dried compound showed no significant change. The dried product melted at 145-147°C (dec) in open capillary and at 154-156°C (dec) under argon in a sealed capillary tube. ^1H NMR (DMSO-d_6) δ 9.65 (br s, 1 H, D_2O exchangeable), 8. 68 (d, J=4.2 Hz, 1 H, QH-2), 7.87 (s, 3 H, D_2O exchangeable), 7.76 (s, 1 H, QH-7), 7.37 (d, J=4.4 Hz, 1 H, QH-3), 3.99 (s, 3 H, OCH_3), 3.90 (m, 1 H, NCH), 2.94 (s, 3 H, QCH_3) 2.81 (m, 2H, NCH_2), 1.85-1.55 (m, 4 H, CH_2CH_2), 1.29 (d, J=6.4 Hz, 3 H, $CHCH_3$).

Anal. Calcd for $C_{16}H_{23}N_3O_2 \cdot 2HBr$ (451.22): C, 42.59; H, 5.58; Br, 35.42, N, 9.31. Found: C, 42.74; H, 5.62; Br, 35.68; N, 9.25.

Thin-Layer Chromatography Analtech HPTLC-RPSF

Eluent	Rf	Comment
Methanol-0.2 M NaH_2PO_4-47% HBr (4:5:0.1)	0.55	Slight streaking

Materials

Compound 5b	Ash Stevens Inc., Lot No. CT-7-49
Palladium black	Aldrich, Lot No. BZ06115BY
Methanol	Mallinckrodt, Lot No. 3016KPEP
Ethanol	Aaper Alcohol, Lot No. 0295R
Petroleum ether (bp 35-60°C)	EM Science, Lot No. 31133135
Isopropanol	Chempure, Lot No. M158KPHA

4.9 N,N-Dimethyl-2-fluoro-5-(trifluoromethyl)benzene-sulfonamide (WR 280649)

2-Fluoro-5-(trifluoromethyl)benzenesulfonyl chloride: - To an ice-cooled and stirred mixture of concd hydrochloric acid (10 mL) and acetic acid (3 mL) was added 3-amino-4-fluorobenzotrifluoride (5.01 g, 30 mmol) in one portion. A white salt precipitated immediately. The mixture was cooled to -10°C, and a solution of sodium nitrite (2.28 g, 33 mmol) in water (3.3 mL) was added at such a rate that the temperature of the reaction mixture did not exceed -5°C. After the addition was completed, the mixture was stirred at -10°C to -5°C for 45 min.

Acetic acid (30 mL) was saturated with sulfur dioxide at room temperature and cuprous chloride (0.75 g) was added to the solution. The introduction of sulfur dioxide was continued until the yellow-green suspension became blue-green (ca. 30 min). The mixture was then cooled to 10°C with ice-water, and the diazonium salt mixture was added in portions over 15 min. Considerable foaming occurred after each addition. The temperature of the reaction mixture was maintained at 7-8°C during the course of addition. After the addition of the diazonium salt mixture was completed, the mixture was poured into ice-water (1:1, 100 mL). The product was extracted from the aqueous solution with ether (2 x 100 mL, 2 x 50 mL). The last extraction was almost colorless. The combined extract was washed with saturated aq. $NaHCO_3$ until neutral (1 x 100 mL, 5 x 50 mL), and then brine (1 x 100 mL). The ether layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure (aspirator). The residue was chromatographed over silica gel (80 g) eluting with a mixture of ether and petroleum ether (1:9). The product-containing fractions were

combined and concentrated (aspirator, and then oil pump) to a light brown oil (5.6 g) which solidified in the freezer but melted at room temperature. The infrared spectrum of the oil was consistent with the chemical structure of the sulfonyl chloride. The oil also gave a positive Beilstein test. The compound was used as such in the next step without further purification.

Materials

3-Amino-4-fluorobenzo-trifluoride	Marshallton, Lot No. 39-265
Acetic acid	CMS Chempure, Lot No. M002KPRS
Hydrochloride acid	Mallinckrodt, Lot No. H613KMBJ
Sodium nitrite	Fluka, Lot No. 331698-1-296
Cuprous chloride	Fluka, Lot No. 350172-1-1095
Sulfur dioxide	Liquid Carbonic Co., no Lot No
Ethyl ether	CMS Chempure, Lot No. M102KPNK
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. K03739
Sodium bicarbonate	Aldrich, Lot No. BG00729LF
Silica gel	EM Science, Lot No. TA770634-516
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161

N,N-Dimethyl-2-fluoro-5-(trifluoromethyl)benzenesulfonamide (WR 280649): - To an ice-cooled and stirred mixture of 2-fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (2.0 g, 7.6 mmol) and dimethylamine hydrochloride (0.62 g, 7.6 mmol) in methylene chloride (20 mL) was added diisopropylethylamine (2.9 g, 22.8 mmol) in one portion. The mixture was stirred in an ice bath for 40 min and poured into ice water (20 mL). The layers were separated and the aq. layer was extracted with methylene chloride (1 x 10 mL). The combined methylene chloride extract was washed with aq. saturated oxalic acid solution (1 x 20 mL), water (1 x 20 mL), brine (1 x 20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure (aspirator, and then vacuum pump) to give crude product (1.9 g) as a yellow solid. The solid was dissolved in warm ethyl ether (5 mL) and the solution was filtered. The clear filtrate was diluted with petroleum ether (7 mL) and refrigerated for 1 h. The mixture was filtered and the solid was dried to give 1.43 g (69%) of pure product in the form of white crystals, mp 67.5-68.5°C. ^{1}HNMR ($CDCl_3$) δ 8.17 (dd, J=2.3, 6.0 Hz, 1 H, H-6), 7.88-7.83 (m, 1 H, H-4), 7.37 (app t, J=9.0 Hz, 1 H, H-3), 2.89 (s, 3 H, N-CH_3), 2.88 (s, 3 H, N-CH_3).

Anal. Calcd for $C_9H_9F_4NO_2S$ (271.24): C, 39.85; H, 3.34; F, 28.02; N, 5.17; S, 11.82. Found: C, 39.89; H, 3.47; F, 28.17; N, 5.10; S, 11.82.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Toluene-ether (4:1)	0.70	Homogeneous

Materials

2-Fluoro-5-(trifluoromethyl)-benzenesulfonyl chloride	Ash Stevens Inc., Lot No. CT-7-86
Dimethylamine hydrochloride	Aldrich, Lot No. TF01504KZ
Diisopropylethylamine	Aldrich, Lot No. HK2318DK
Methylene chloride	J.T. Baker, Lot No. J51613
Oxalic acid	Aldrich, Lot No. LY01624HY
Ethyl ether	CMS Chempure, Lot No. 102KPNK
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. K03739
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161

4.10 2-Fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (WR 280675)

A 200 mL 3-necked flask equipped with a mechanical stirrer, thermometer, and a dropping funnel was charged with concd hydrochloric acid (43 mL) and acetic acid (13 mL). With ice-cooling, 3-amino-4-fluorobenzotrifluoride (21.5 g, 128.7 mmol) was added in one portion. A white solid formed immediately. The mixture was cooled to below -10°C and a solution of sodium nitrite (9.8 g, 142.0 mmol) in water (14 mL) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed -5°C. After the addition was completed, the mixture was stirred at -10°C to -5°C for 45 min.

A separate 500 mL 3-necked flask equipped with a mechanical stirrer and a gas inlet tube was charged with acetic acid (129 mL). At room temperature, sulfur dioxide was bubbled into the solvent until saturation (ca. 15 min), then cuprous chloride (3.2 g) was added to the solution. The introduction of sulfur dioxide was continued until the yellow-green solution became blue-green (ca. 30 min). The gas inlet tube was replaced by a thermometer. The mixture was cooled to 10°C (ice bath), and the diazonium salt mixture was added in portions. Considerable foaming occurred after each addition. The temperature of the reaction mixture was maintained at 7-8°C. After the addition of the diazonium salt was completed, the mixture (green in color) was poured into ice-water (1:1, 400 mL), and the quench was extracted with ether (2 x 400 mL, 2 x 200 mL). The last extraction was almost colorless. The combined ether extract was washed with cold water (5 x 400 mL), cold satd aqueous $NaHCO_3$ (2 x 400 mL), cold brine (1 x 400 mL), and dried ($MgSO_4$, 70 g). The mixture was filtered and the filtrate was concentrated under reduced pressure (aspirator, and then vacuum pump) to give a brown oil (25.6 g).

In the same manner, another lot of 3-amino-4-fluorobenzotrifluoride (25 g) was processed to give 30.5 g of crude product as a brown oil. The combined product (25.6 g, + 30.5 g) was chromatographed over silica gel (400 g) and the column was eluted with a mixture of ether-petroleum ether (1:9). Fractions containing product were combined and concentrated (aspirator) to give a brown oil (49.5 g). The oil was distilled to yield 43.9 g (60%) of pure target compound as a yellow clear liquid, bp 72-76°C/0.7 mmHg. The liquid solidified in the freezer. ^{1}H NMR ($CDCl_3$) δ 8.27 (dd, J=1.95, 6.02 Hz, 1 H), 8.10-8.05 (m, 1 H), 7.55 (t, J=8.77 Hz, 1 H).

Anal. Calcd for $C_7H_3ClF_4O_2S$ (262.61): C, 32.02; H, 1.15; Cl, 13.50; F, 28.94; S, 12.21. Found: C, 31.96; H, 1.10; Cl, 13.55; F, 28.97; S, 12.13.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Ether-petroleum ether (1:9)	0.51	Trace impurity at origin

Materials

3-Amino-4-fluorobenzotrifluoride	Marshallton, Lot No. 39-265
Acetic acid	CMS Chempure, Lot No. M002KPRS
Hydrochloric acid	Mallinckrodt, Lot No. H613KMBJ
Sodium nitrite	Fluka, Lot No. 331698-1-296
Cuprous chloride	Fluka, Lot No. 350172-1-1095
Sulfur dioxide	Liquid Carbonic Co., no Lot No
Ethyl ether	CMS Chempure, Lot No. M102KPNK
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. K03739
Sodium bicarbonate	Aldrich, Lot No. BG00729LF
Silica Gel	EM Science, Lot No. TA770634-516
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161

4.11 8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-hydroxy-4-methylquinoline dihydrochloride (WR 280682)

The synthesis route to the title compound is shown in Chart No. 6.

5-Hydroxy-6-methoxy-4-methyl-8-nitroquinoline (1): - This starting material was prepared by the previously described procedure (5).

5-Chloro-6-methoxy-4-methyl-8-nitroquinoline (2): - Following the previously described procedure, 5-hydroxyquinoline 1 (216.3 g) was treated with phosphorus oxychloride to give 191.3 g (82%) of the title 5-chloroquinoline 2, mp 167-169°C; lit. mp 167-169.5°C (4).

5-Chloro-6-hydroxy-4-methyl-8-nitroquinoline (3): - Anhydrous aluminum chloride (79.6 g, 0.6 mol) was added to a warm (55°C) solution of 5-chloroquinoline 2 (80.3 g, 0.32 mol) in 1,2-dichloroethane (650 ml) under a nitrogen atmosphere. The mixture instantly turned blood-red. The mixture was heated at 60-65°C for 30 min, then crushed ice (1 L) and concd hydrochloric acid (160 mL) were added. The dark solid in the mixture was broken up manually and the mixture was diluted further with water (1 L) and stirred for 30 min. The light brown solid was collected by filtration (polyethylene filter-aid), washed with water (3 x 200 mL) and air-dried for 20 h to give crude title compound, 86.5 g. The crude product was dissolved in 5% aqueous sodium hydroxide (600 mL) and the dark solution was diluted with water (1.2 L). The solution was stirred for 30 min and filtered through a pad of celite. The filtrate was acidified to pH ca. 5 with glacial acetic acid (180 mL) and the mixture was stirred for 1 h. The beige solid was collected by filtration, washed with water (2 x 100 mL) and dried at 50°C/0.1 mmHg for 18 h to give 63 g of purified title compound.

Additional 5-chloroquinoline 2 (85.2 g) was processed in this manner to give 68.8 g of purified product.

The combined purified product (131.8 g) was dissolved in hot toluene (4.5 L). The solution was treated with charcoal (ca. 6 g), filtered through a pad of celite using a jacketed steam-heated funnel, and the volume of the filtrate was reduced to ca. 3 L (40-45°C/aspirator). The warm concentrate was diluted with hexanes (2 L) and the mixture was stirred at room temperature for 1 h. The solid was collected by filtration, washed with hexanes (500 mL) and dried at 50°C/0.1 mmHg for 18 h to give pure title compound 3, 119.6 g (76%), mp 159-160°C; ^{1}H NMR (DMSO-d_6) δ 11.39 (s, 1 H, OH), 8.57 (d, J=4.2 Hz 1 H, QH-2), 7.87 (s, 1 H, QH-7), 7.41 (d, J=3.9 Hz, 1 H, QH-3), 2.92 (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_7ClN_2O_3$ (238.63): C, 50.33; H, 2.96; Cl, 14.86; N, 11.74. Found: C, 50.49; H, 2.92; Cl, 14.81; N, 11.59.

Thin-Layer Chromatography: EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:3)	0.22	Major
	0.03	Trace

Materials

Compound 2	Ash Stevens Inc., Lot Nos. DJD-14-125, -14-224
1,2-Dichloroethane	Fisher Scientific, Lot No. 952553
Aluminum chloride, anhydrous	Aldrich, Lot Nos. HN12302BN and AQ07123EN
Hydrochloric acid	Mallinckrodt, Lot No. H613KMMB
Sodium hydroxide	Mallinckrodt, Lot No. 7708KPNM
Water, deionized	Ash Stevens Inc., no Lot No.
Acetic acid, glacial	Chempure, Lot No. M002KPRS
Toluene	J.T. Baker, Lot No. J49621
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Celite, tech	Celite Corp., Lot No. C5453AP301016
Hexanes	Fisher Scientific, Lot No. 952852

6-Benzyloxy-5-chloro-4-methyl-8-nitroquinoline (4): - A stirred mixture of 6-hydroxyquinoline 3 (119.5 g, 0.5 mol), benzyl bromide (109.5 g, 0.64 mol), 40 wt% aqueous tetrabutylammonium hydroxide (402.5 g, 0.62 mol), water (250 mL) and toluene (2 L) was heated at 65-70°C for 90 min. Analysis by TLC (Analtech, EtOAc-hexanes 1:3) showed the absence of starting material. The layers were separated and the aqueous layer was extracted with toluene (750 mL). The combined organic phase, upon cooling to room temperature, deposited a solid. The mixture was diluted with ethyl acetate (1.5 L) to dissolve the solid. The solution was washed with water (1.5 L), dried (magnesium sulfate) and filtered. The filtrate was concentrated to dryness (50-55°C/aspirator) and the solid residue was dried at 40°C/0.1 mmHg for 1 h to give crude title compound, 158.8 g. The crude product was dissolved in hot toluene (500 mL). The solution was diluted with hot hexanes (2 L) and allowed to cool to room temperature over 2 h. The beige solid was collected by filtration and dried at 60°C/0.1 mmHg for 2 h to give pure compound 4, 142.9 g (87%), mp 148-150°C. ^1H NMR (DMSO-d_6) δ 8.65 (d, J=4.2 Hz, 1 H, QH-2) 8.49 (s, 1 H, QH-7), 7.55-7.26 (m, 6 H, QH-3 and ArH), 5.38 (s, 2 H, $ArCH_2$), 2.94 (s, 3 H, QCH_3).

Anal. Calcd for $C_{17}H_{13}ClN_2O_3$ (328.76): C, 62.11; H, 3.99; Cl, 10.78; N, 8.52. Found: C, 61.95; H, 3.95; Cl, 11.11; N, 8.40.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:3)	0.54	Homogeneous

Materials

Compound 3	Ash Stevens Inc., Lot No. DJD-14-226
Benzyl bromide	Aldrich, Lot No. MZ09315LZ
Tetrabutylammonium hydroxide, 40 wt% in water	Aldrich, Lot No. PN11622KN
Toluene	J.T. Baker, Lot No. J30661
Ethyl acetate	Fisher Scientific, Lot No. 952846
Water, deionized	Ash Stevens Inc., no Lot No.
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Hexanes	Fisher Scientific, Lot No. 952852

6-Benzyloxy-5-methoxy-4-methyl-8-nitroquinoline (5): - Compound 4 (142.8 g, 0.43 mol) was added to a solution of sodium methoxide (103.8 g, 1.92 mol) in methanol (7 L) and the mixture was heated at reflux for 72 h, then methanol (2 L) was removed by distillation. Analysis by TLC (Analtech, toluene-acetone, 9:1) showed only a trace of starting material present. The dark solution was cooled to room temperature, acidified to pH ca 5-6 with glacial acetic acid (140 mL) and concentrated to dryness (40-45°C/aspirator). The semisolid residue was dissolved in a mixture of dichloromethane (2 L) and water (1.5 L). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 500 mL). The combined organic phase was washed with water (1 L), dried (magnesium sulfate), and filtered through a pad of celite. The filtrate was concentrated to a volume of ca. 750 mL (ca. 30°C/aspirator) and chromatographed over silica gel (635 g, 20 x 9 cm). The column was eluted with dichloromethane (6 L). The product-containing fractions were combined and concentrated to dryness (ca. 35-40°C/aspirator). The solid residue was stirred with hexanes (750 mL) for 1 h and the mixture was filtered. The light yellow solid was air-dried for 72 h to give pure title compound 5, 115.3 g (82%), mp 105-107°C. An analytical sample was prepared by recrystallization from toluene-hexanes (1:5), mp 106-108°C. ^{1}H NMR ($CDCl_3$) δ 8.72 (d, J=4.5 Hz, 1 H, QH-2), 7.89 (s, 1 H, QH-7), 7.55-7.35 (m, 5 H, ArH), 7.22 (dd, J=0.9, 4.2 Hz, 1 H, QH-3), 5.25 (s, 2 H, $ArCH_2$), 4.03 (s, 3 H, OCH_3), 2.91 (s, 3 H, QCH_3).

Anal. Calcd for $C_{18}H_{16}N_2O_4$ (324.34): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.52; H, 5.02; N, 8.63.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:3)	0.42	Major
	0.56	Trace

Materials

Compound 4	Ash Stevens Inc., Lot No. DJD-14-228
Sodium methoxide	Aldrich, Lot No. HN10515EN
Methanol	Chempure, Lot No. M178KMDH
Dichloromethane	J.T. Baker, Lot No. H40639
Water, deionized	Ash Stevens Inc., no Lot No.
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Celite, tech	Celite Corp., Lot No. C5453AP301016
Silica gel	EM Science, Lot No. TA572034418
Hexanes	Fisher Scientific, Lot No. 952852

6-Benzyloxy-5-hydroxy-4-methyl-8-nitroquinoline (6): - Concd hydrochloric acid (114 mL) was added to a warm (ca. 60°C) solution of compound 5 (114 g, 0.35 mol) in ethanol (1.5 L) and the mixture was heated at reflux for 24 h. The mixture was cooled to room temperature and filtered. The brick-red solid was washed with ethanol (2 x 250 mL) followed by hexanes (2 x 250 mL) and dried at 70°C/0.1 mmHg for 3 h to give pure title compound 6, 96.6 g (88%), mp 246-248°C dec.

Anal. Calcd for $C_{17}H_{14}N_2O_4$ (310.31): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.72; H, 4.54; N, 8.84.

Materials

Compound 5	Ash Stevens Inc., Lot No. DJD-14-230
Ethanol	Aaper Alcohol, Lot No. 0295R
Hydrochloric acid	Mallinckrodt, Lot No. H613KMMB
Hexanes	Fisher Scientific, Lot No. 952852

6-Benzyloxy-5-(1-hexyloxy)-4-methyl-8-nitroquinoline (7): - A stirred mixture of compound 6 (96.4 g, 0.40 mol), 1-bromohexane (113 g, 0.68 mol), 40 wt% aqueous tetrabutylammonium hydroxide (397 g, 0.61 mol), water (250 mL) and toluene (2 L) was heated at 80-82°C for 40 h. At 17 h and again at 25 h, additional 1-bromohexane (43 g, followed by 50 g, 0.56 mol total) and tetrabutylammonium hydroxide (112 g followed by 152 g, 0.41 mol total) were added to the mixture. After 40 h, the mixture was cooled to ca. 50°C and the layers were separated. The aqueous layer was extracted with toluene (2 x 500 mL). The combined organic phase was washed with warm (ca. 60°C) water (2 x 1 L) and dried (magnesium sulfate). The dark solution was filtered through a pad of celite and the filtrate was concentrated to dryness (45-50°C/aspirator). The solid residue (138.5 g) was dissolved in dichloromethane (250 mL) and chromatographed over silica gel (520 g, 18.5 x 9 cm). The column was eluted with dichloromethane (6 L). The product-containing fractions were combined and saved. The forecut and later fractions were combined, concentrated to dryness and rechromatographed over silica gel as above. The product-containing fractions from both chromatographies were combined and concentrated to dryness (35-40°C/aspirator). The solid was dried further at 25°C/0.1 mmHg for 18 h to give purified title compound, 79 g. The purified product was dissolved in warm anhydrous ether (500 mL). The solution was treated with charcoal (4.5 g) and filtered through a pad of celite. The filtrate was refiltered (gravity) and the volume of the solution was reduced to ca. 200 mL (30-35°C/aspirator). Petroleum ether (800 mL) was added and the mixture was cooled in an ice bath for 90 min. The light yellow-orange solid was collected by filtration and air-dried for 20 h to give pure title compound 7, 72 g (59%), mp 57-59°C. ^{1}H NMR (DMSO-d_6) δ 8.61 (d, J=4.5 Hz, 1 H, QH-2), 8.40 (s, 1 H, QH-7), 7.48 (d, J=7.5 Hz, 2 H, ArH), 7.45-7.28 (m, 4 H, ArH and QH-3), 5.27 (s, 2 H, $ArCH_2$), 4.03 (t, J=6.9 Hz, 2 H, OCH_2), 2.80 (s, 3 H, QCH_3), 1.66 (quint, J=7.2 Hz, 2 H, $OCH_2\underline{CH_2}$), 1.36-1.10 (m, 6 H, $(CH_2)_3$), 0.78 (t, J=6.6 Hz, 3 H $CH_2\underline{CH_3}$).

Anal. Calcd for $C_{23}H_{26}N_2O_4$ (394.47): C, 70.03; H, 6.64; N, 7.10. Found: C, 70.29; H, 6.63; N, 7.13.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:3)	0.61	Major
	0.71	Trace

Materials

Compound 6	Ash Stevens Inc., Lot No. DJD-14-233
Toluene	J.T. Baker, Lot No. J30661
Tetrabutylammonium hydroxide, 40 wt% in water	Aldrich, Lot Nos. PN11622KN and AQ11622KN
1-Bromohexane	Fluka, Lot No. 339662/1 1195
Water, deionized	Ash Stevens Inc, no Lot No.
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Dichloromethane	J.T. Baker, Lot Nos. J28652 and H40639
Silica gel	EM Science, Lot No. TA572034 418
Ether, anhydrous	J.T. Baker, Lot No. H28622
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. H05616
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Celite, tech	Celite Corp., Lot No. C5453AP301016
Celite, analytical	Celite Corp., no Lot No.

8-Amino-6-benzyloxy-5-(1-hexyloxy)-4-methylquinoline (8): - Iron powder (30.3 g, 0.54 mol) was added to a warm (ca. 45°C) solution of compound 7 (32 g, 0.08 mol) in glacial acetic acid (105 mL) and the mixture was heated to ca. 60°C (steam bath) under a nitrogen atmosphere. After 2-3 min at this temperature, the mixture exothermed to ca. 105°C. The mixture was allowed to cool over 25 min to ca. 60°C at which time TLC (Analtech, EtOAc-hexanes, 1:3) showed the reaction to be complete. The mixture was diluted with ethyl acetate (1 L) and water (1 L) and filtered through a pad of celite. The filtrate was transferred to a separatory funnel and the layers were separated. The organic layer was washed with deionized water (1 L), saturated sodium bicarbonate solution (2 x 500 mL) and saturated sodium chloride solution (500 mL). All of the aqueous layers were backwashed successively with ethyl acetate (500 mL). The combined organic layer was dried (magnesium sulfate), treated with charcoal, and filtered through a pad of celite. The filtrate was concentrated to dryness (35-40°C/aspirator) and the residue was dried further at 25°C/0.1 mmHg for 1 h to give crude product, 28.9 g. The crude solid product was dissolved in ethyl acetate-hexanes (1:5, 200 mL) and chromatographed over silica gel (310 g, 30 x 5.5 cm). The column was eluted with ethyl acetate-hexanes (1:5, 2 L; 1:4, 2 L; 3:7, 2 L). The product-containing fractions were combined and concentrated to dryness (35-40°C/aspirator) to give purified title compound, 24.4 g.

Additional compound 7 (39.7 g) was processed in this manner to give 27.6 g of purified product 8.

The combined purified product (52 g) was dissolved in hot petroleum ether (600 mL). The solution was treated with charcoal (3 g), and filtered through a pad of celite. The filtrate was refiltered (gravity), concentrated to a volume of ca. 500 mL (30-35°C/aspirator), and cooled in an ice-bath for 2 h. The yellow spongy solid was collected by filtration, pressed to remove most of the solvent, and dried immediately at 35°C/0.1 mmHg for 1 h to give pure title compound 8, 38.2 g (58%), mp 53-55°C. The analytical sample was obtained from a probe reduction and had the same melting point. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J=4.2 Hz, 1 H, QH-2), 7.55-7.30 (m, 5 H, ArH), 7.09 (d, J=4.2 Hz, 1 H, QH-3), 6.78 (s, 1 H, QH-7), 5.18 (s, 2 H, $ArCH_2$), 4.91 (br s, 2 H, NH_2), 3.95 (t, J=6.9 Hz, 2 H, OCH_2), 2.89 (s, 3 H, QCH_3), 1.81 (quint J=7.2 Hz, 2 H, OCH_2CH_2), 1.53-1.20 (m, 6 H, $(CH_2)_3$), 0.89 (t, J=6.6 Hz, 3 H, CH_2CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_2$ (364.49): C, 75.79; H, 7.74; N, 7.69. Found: C, 75.78; H, 7.79; N, 7.70.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:3)	0.33	Homogeneous

Materials

Compound 7	Ash Stevens Inc., Lot No. DJD-14-235
Acetic acid, glacial	Chempure, Lot No. M002KPRS
Iron powder	Fluka, Lot No. 330655/1 995
Ethyl acetate	Fisher Scientific, Lot No. 952846
Water, deionized	Ash Stevens Inc., no Lot No.
Sodium chloride, food grade	no Lot No.
Sodium bicarbonate	FMC Corp., Lot No. 92-358
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Celite, tech	Celite Corp., Lot No. C5453AP301016
Hexanes	J.T. Baker, Lot No. K08776
Silica gel	EM Science, Lot No. TA784834519
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. H05616

6-Benzyloxy-5-(1-hexyloxy)-4-methyl-8-[(1-methyl-4-phthalimidobutyl)amino]quinoline (9): - A solution of compound 8 (38.1 g, 0.10 mol), 4-iodo-1-phthalimidopentane (43.2 g, 0.13 mol) and diisopropylethylamine (22.5 mL, 0.13 mol) in acetonitrile (250 mL) was heated under a nitrogen atmosphere at reflux for 41 h. At 17 h and again at 25 h additional 4-iodo-1-phthalimidopentane (26.8 g followed by 27.5 g, 0.16 mol total)

and diisopropylethylamine (13.2 mL followed by 13.5 mL, 0.15 mol total) were added to the mixture. After 41 h, the mixture was cooled to room temperature and diluted with water (1 L) and ether 500 mL). The layers were separated and the aqueous layer was extracted with ether (500 mL). The combined ether layer was washed with saturated sodium chloride solution (250 mL), dried (magnesium sulfate), and treated with charcoal. The dark red-brown solution was filtered through a pad of celite and the filtrate was concentrated (30-35°C/aspirator) to an oil, 113.8 g. The oil was dissolved in ethyl acetate-hexanes (1:3, 400 mL) and charged onto a silica gel column (900 g, 37 x 9 cm, packed in ethyl acetate-hexanes, 1:9). The column was eluted with ethyl acetate-hexanes (1:9, 5 L; 1.25:8.75, 2 L; and 1.5:8.5, 2 L) to remove faster impurities and slightly impure-product, 37 g. Further elution (1.75:8.25, 1 L; 1:4, 2.5 L, 1:3, 2 L) gave pure product-containing fractions which were saved. The impure product, 37 g, was rechromatographed over silica gel (315 g, 30 x 5.5 cm) to give additional pure product-containing fractions. All product-containing fractions were combined and concentrated (35-40°C, aspirator, then at 40°C/0.1 mmHg for 1 h) to give purified title compound 9, 57.2 g (94%) in the form of an orange-red syrup. Attempts to obtain the product in solid form, failed. This intermediate was used as such in the next step.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:3)	0.48	Homogeneous

Materials

Compound 8	Ash Stevens Inc., Lot No. DJD-14-239
4-Iodo-1-phthalimidopentane	Ash Stevens Inc., Lot No. DAG-05-165
Diisopropylethylamine, distilled prior to use	Ash Stevens Inc., Lot No. DAG-02-50
Acetonitrile	Burdick and Jackson, Lot No. BF350
Ether	J.T. Baker, Lot No. J33659
Water, deionized	Ash Stevens Inc., no Lot No.
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Celite, tech	Celite Corp., Lot No. C5453AP301016
Sodium chloride, food grade	no Lot No.
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Silica gel	EM Science, Lot No. TA784834519
Ethyl acetate	J.T. Baker, Lot No. J48617
Hexanes	J.T. Baker, Lot No. K08776

8-[(4-Amino-1-methylbutyl)amino]-6-benzyloxy-5-(1-hexyloxy)-4-methylquinoline dihydrochloride (10): - Anhydrous hydrazine (25.3 g, 0.79 mol) was added to a warm (40-45°C) solution of compound 9 (57.2 g, 0.099 mol) in ethanol (1.25 L) under a nitrogen atmosphere. The mixture was heated at reflux for 75 min, then cooled to ca. 40°C. The deposited phthalhydrazide was collected by filtration, washed with ethanol (3 x 125 mL) and discarded. Deionized water (30 mL) was added to the filtrate which was then concentrated to dryness (55-60°C/ aspirator). The residue was mixed with dichloromethane (750 mL) and 4 N aqueous sodium hydroxide solution (500 mL). The layers were separated and the organic phase was washed with 4 N aqueous sodium hydroxide solution (250 mL). The combined aqueous layer was backwashed with dichloromethane (250 mL). The combined organic layer was dried (potassium carbonate), treated with charcoal (2 g), and filtered through a pad of celite. The filtrate was concentrated (ca. 30°C/aspirator) to an oil, 44.2 g. The oil was dissolved in dichloromethane (100 mL) and chromatographed over silica gel (200 g, 18 x 5.5 cm). The column was washed with dichloromethane (500 mL), 1% MeOH-CH_2Cl_2 (500 mL), and 2% MeOH-CH_2Cl_2 (500 mL) to remove impurities. Elution with 3% MeOH-CH_2Cl_2 (500 mL) and 4%MeOH-CH_2Cl_2 (500 mL) gave slightly impure product (18 g). Further elution with MeOH-CH_2Cl_2 (1:9, 500 mL; 1:4, 500 mL; 3:7, 500 mL) gave pure product-containing fractions which were saved. The impure-product (18 g) was rechromatographed as above and gave additional product-containing fractions. All product-containing fractions were combined and the solvent was removed (35-40°C/aspirator, then at 25°C/0.1 mmHg for 18 h) to give 38.8 g of purified compound 10 free base in the form of an oil.

Ethanolic hydrogen chloride (6.8 N, 30 mL, 0.2 mmol) was added to a solution of the free base (38.8 g, 0.086 mol) in ethanol (350 mL). The resulting blood-red solution was concentrated to a volume of ca. 180 mL (50-55°C/aspirator) and diluted with 2-propanol (800 mL). The slurry was heated to dissolve the solid and the solution was filtered (gravity). The filtrate was allowed to cool to room temperature and then cooled in an ice bath for 90 min. The bright, brick-red solid was collected by filtration, washed with hot petroleum ether (2 x 250 mL), and dried at 55°C/0.1 mmHg for 3.5 h and at 25°C/0.1 mmHg for 16.5 h to give pure title compound 10, 36.6 g (71%), mp 197-199°C. A sample of product obtained from a probe reaction, mp 195-198°C, was submitted for analysis. ^{1}H NMR (DMSO-d_6) δ 8.55 (d, J=4.8 Hz, QH-2), 8.12 (br s, 3 H, NH_3), 7.6-7.25 (m, 6 H, ArH and QH-3), 7.14 (br s, 1 H, QH-7), 5.31 (s, 2 H, $ArCH_2$), 3.90 (t, J=6.4 Hz, 2 H, OCH_2), 3.79 (m, 1 H, NCH), 2.89 (s, 3 H, QCH_3), 2.74 (m, 2 H, CH_2N), 1.67 (m, 6 H, $NCH\underline{CH_2CH_2}$ and $OCH_2\underline{CH_2}$), 1.4-1.1 (m, 9 H, $CH\underline{CH_3}$, $(CH_2)_3$), 0.79 (t, J=6.9 Hz, 3 H, $CH_2\underline{CH_3}$).

Anal. Calcd for $C_{28}H_{41}Cl_2N_3O_2$ (522.56): C, 64.36; H, 7.91; Cl, 13.57; N, 8.04. Found: C, 64.53; H, 8.06; Cl, 13.81; N, 8.12.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Methylene chloride-methanol-acetic acid-water (88:10:1:1)	0.36	Homogeneous

Materials

Compound 9	Ash Stevens Inc., Lot No. DJD-14-241
Ethanol	Baxter Diagnostics, Lot No. 6038
Hydrazine, anhydrous	Aldrich, Lot No. MF07326MF
Water, deionized	Ash Stevens Inc., no Lot No.
Dichloromethane	J.T. Baker, Lot No. H40639
Sodium hydroxide	J.T. Baker, Lot No. H07728
Potassium carbonate, anhydrous	J.T. Baker, Lot No. D49104
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Celite, tech	Celite Corp., Lot No. C5453AP301016
Silica gel	EM Science, Lot No. TA784834519
Methanol	Mallinckrodt, Lot No. 3016KTBK
Hydrogen chloride, gas	Matheson Gas, Lot No. T310128
2-Propanol	Fisher Scientific, Lot No. 911757
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. H05616

8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-hydroxy-4-methylquinoline dihydrochloride, half hydrate (WR 280682)(11): - All solvents used in this step were freed of gaseous oxygen prior to use. Product isolation and purification was conducted under argon atmosphere.

Palladium-black catalyst (1.54 g) was added to a warm (40-45°C) solution of compound 10 (6.55 g, 12.5 mmol) in ethanol (200 mL). The mixture was hydrogenated at 55 psi for 90 min at which time analysis by TLC (EM Science, Kieselgel 60 F_{254}, MeOH-H_2O-HOAc-CH_2Cl_2, 10:1:1:88) showed the reaction to be complete. The mixture was filtered through a pad of celite and the bottle as well as the celite pad were washed with ethanol (2 x 15 mL). The combined dark red filtrate was concentrated to dryness (35-40°C/0.1 mmHg). The residue was dissolved in warm (30-40°C) ethanol (30 mL), cooled to room temperature, then diluted with petroleum ether (60 mL) and allowed to stand undisturbed at room temperature for 18 h. The orange-red solid was collected by filtration, washed with ethanol-petroleum ether (1:3, 25 mL)

followed by petroleum ether (2 x 25 mL), and dried at 25°C/0.1 mmHg for 20 h to give purified product, 4.74 g.

Additional compound 10 (8.59 g) was processed in this manner to give 6.28 g of purified product.

The combined purified product (11 g) was dissolved in warm (45-48°C) ethanol (66 mL). The dark red solution was allowed to cool to room temperature and diluted with petroleum ether (30 mL). Without disturbing the crystalline product, the mixture was diluted carefully with ethanol-petroleum ether (1:1, 30 mL) after 1 h and (1:2, 30 mL) after 3 h. After 5 h the bright red solid was collected by filtration, washed successively with ethanol-petroleum ether (1:2, 50 mL) followed by petroleum ether (2 x 75 mL), and dried at 25°C/0.1 mmHg for 32 h to give 8.33 g of product, mp 125-127°C. Elemental analysis and NMR indicated that the compound contained ethanol and water of solvation. This material (7.94 g) was dried further at 60°C/0.1 mmHg for 5 h to give 7.72 g (60%) of pure product as a half-hydrate, mp 126-128°C. ^{1}H NMR (DMSO-d_6) δ 10.33 (br s, 1 H, OH), 8.50 (d, J=5.1 Hz, 1 H, QH-2), 8.03 (br s, 3 H, NH), 7.46 (d, J=4.8 Hz, 1 H, QH-3), 7.12 (s, 1 H, QH-7), 3.88 (t, J=6.6 Hz, 2 H, OCH_2), 3.56 (m, 1 H, NCH), 2.89 (s, 3 H, QCH_3), 2.85-2.70 (m, 2 H, CH_2N), 1.85-1.55 (m, 6 H, CH_2), 1.45-1.22 (m, 6 H, CH_2), 1.22 (d, J=6.0 Hz, 3 H, $CHCH_3$), 0.84 (t, J=6.9 Hz, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{33}N_3O_2 \cdot 2HCl \cdot 1/2\ H_2O$ (441.44): C, 57.14; H, 8.22; Cl, 16.06; N, 9.52. Found: C, 57.05; H, 8.08; Cl, 16.09; N, 9.52.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Methylene chloride-methanol-acetic acid-water (88:10:1:1)	0.15	Slight streaking

Materials

Compound 10	Ash Stevens Inc., Lot No. DJD-14-244
Ethanol	Baxter Diagnostics, Lot No. 6038
Palladium black	Aldrich, Lot No. KN15710KN
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. H05616
Celite, tech	Celite Corp., Lot No. C5453AP301016
Argon gas	Airco, grade 4.8, Cylinder No. 242906X
Hydrogen gas	Airco, grade 5.0, no Lot No.

4.12 Resolution of racemic α-[2-(Butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol

4.12.1 (+)-α-[(2-(Butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol hydrochloride (WR 280823)

A solution of dl-α-[2-(butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol hydrochloride (4.5 g, 9.36 mmol) in warm methanol (60 mL) was passed through a column of Dowex 2-X8 base form ion-exchange resin (100 mL, 1.2 meq/mL, 2 cm x 35 cm). Fractions containing product were combined and evaporated (aspirator) to give a cream-colored solid (4.16 g, quantitative). A warm solution of this free amine in methanol (42 mL) was mixed with a solution of di-p-toluoyl-L-tartaric acid (3.62 g, 9.36 mmol) in ethyl acetate (126 mL). The clear solution was seeded with the resolved salt obtained from a probe resolution and allowed to stand at room temperature overnight, then refrigerated for 5 h. The precipitate was collected by suction filtration to give 3.11 g of crude salt as white solid, mp 174-177°C (dec). The filtrate was saved for preparation of the enantiomer (see below). The white solid (3.11 g) was dissolved in hot methanol (31 mL) and diluted with hot ethyl acetate (93 mL). The solution was allowed to stand at room temperature for 2 h, then stored in a refrigerator for 4 h. The precipitate was collected by filtration to give 2.50 g of salt as white crystals, mp 183-185°C (dec). This salt (2.50 g) was combined with similar salt (1.94 g, mp 185-187°C (dec)) obtained from a previous resolution and dissolved in hot methanol (44 mL). The solution was diluted with hot ethyl acetate (132 mL) and allowed to stand at room temperature for 2 h, then it was refrigerated for 4 h. The precipitate was collected by suction filtration to give 3.85 g of pure salt as white crystals, mp 185-186°C (dec). This salt was dissolved in warm methanol (35 mL) and the solution was passed through a column of base-form Dowex 2-X8 ion-exchange resin (45 mL, 1.2 meq/mL, 2 cm x 16 cm). The product-containing fractions were combined and evaporated (aspirator) to give 2.02 g of product free base, mp 117-119°C, $[\alpha]^{25}_{D}$ + 38.2° (c, 1.03, MeOH).

To an ice-cooled solution of the free base (2.0 g, 4.5 mmol) in methanol (30 mL) was added 10 N ethanolic hydrogen chloride (0.50 mL, 5 mmol) with stirring. A white solid precipitated immediately. The mixture was stirred at room temperature for 10 min, then diluted slowly with ether (30 mL). The mixture was stirred in an ice-bath for 2 h and filtered to give 1.9 g of the hydrochloride salt as a white solid. Concentration of the filtrate gave a second crop (0.19 g) which was set aside. The crude product (1.9 g) was dissolved in boiling methanol (40 mL) and the solution was filtered. The clear filtrate was stirred at room temperature for 10 min, then diluted slowly with ether (40 mL). The mixture was stirred at room temperature for 2 h, cooled in an ice-bath for 2 h, and

stored in a refrigerator overnight. The product was collected by suction filtration and dried at room temperature/0.25 mmHg for 8 h to yield 1.47 g of pure target compound as white crystals, mp 287-288°C (dec), $[\alpha]^{25}_D$ + 51.6° (c, 1.03, MeOH). ^{1}H NMR (DMSO-D_6) δ 9.36 (s, 1 H), 9.21 (s, 1 H), 8.95 (br s, 1 H, D_2O exchangeable), 8.60 (d, J=8.9 Hz, 1 H), 8.48 (s, 1 H), 8.03 (m, 2 H), 6.11 (br s, 1 H, D_2O exchangeable) 5.60 (m, 1 H), 3.22 (m, 1 H), 3.10 (m, 1 H), 2.89 (t, J=7.9 Hz, 2 H), 2.28 (m, 1 H), 2.04 (m, 1 H), 1.62 (m, 2 H), 1.33 (hex, J=7.4 Hz, 2 H), 0.89 (t, J=7.4 Hz, 3 H).

Anal. Calcd for $C_{22}H_{22}Cl_2F_3NO \cdot HCl$ (480.80): C, 54.96; H, 4.82; Cl, 22.12; F, 11.86; N, 2.91. Found: C, 54.75; H, 4.81; Cl, 22.14; F, 11.65; N, 2.90.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Tetrahydrofuran-ether-5% NH_4OH (2:2:0.1)	0.70	Homogeneous

4.12.2 (-)-α-[2-(Butylamino)ethyl]-1,3-dichloro-6-(trifluoromethyl)-9-phenanthrenemethanol hydrochloride (WR 280691)

The filtrate from the L-tartrate salt (see above) was evaporated (aspirator) to near dryness and the residual semi-solid was dissolved in methanol (60 mL). The solution was passed through a column of Dowex 2-X8 base-form ion-exchange resin (60 mL, 1.2 meq/mL) eluting with methanol. Fractions containing product were combined and evaporated (aspirator) to give a faint yellow solid (2.54 g). The solid (2.54 g, 5.71 mmol) was dissolved in hot methanol (25 mL), and the solution was treated with a solution of di-p-toluoyl-D-tartaric acid (2.21 g, 5.71 mmol) in ethyl acetate (75 mL). The clear solution was seeded with pure salt obtained from a probe resolution and allowed to stand at room temperature for 2 h, then refrigerated overnight. The precipitate was collected by suction filtration to yield 3.39 g of salt, mp 179-181°C (dec). The solid was recrystallized from a mixture of methanol (34 mL) and ethyl acetate (102 mL) as described for the (+)-enantiomer above to give 2.78 g of salt, mp 184-186°C (dec). This salt (2.78 g) was combined with similar salt (1.80 g, mp 186-187°C (dec)) prepared earlier and recrystallized from a mixture of methanol (45 mL) and ethyl acetate (135 mL) to give 3.95 g of pure salt as white crystals, mp 185-186°C (dec). The salt was dissolved in hot methanol (35 mL) and the solution was passed through a column of Dowex 2-X8 base-form ion-exchange resin (46 mL, 1.2 meq/mL). The column was eluted with methanol. The product-containing fractions were combined and evaporated (aspirator) to give 2.10 g of free base as a white solid, mp 118-119°C, $[\alpha]^{25}_D$ -38.6° (c, 1.05, CH_3OH). The solid was dissolved in warm methanol (30 mL) and the solution

was filtered. The clear filtrate was cooled in ice-water and treated with 10 N ethanolic hydrogen chloride (0.52 mL, 5.2 mmol). A white solid precipitated immediately. The mixture was stirred at room temperature for 10 min and ether (30 mL) was added slowly to the mixture. The mixture was stirred in an ice bath for 30 min and stored in a refrigerator overnight. The solid was collected by suction filtration to give 2.02 g of the hydrochloride salt. The salt (2.02 g) was dissolved in hot methanol (42 mL) and the solution was filtered. The clear filtrate was stirred at room temperature for 10 min, then diluted slowly with ether (42 mL). The mixture was stirred at room temperature for 2 h, cooled in an ice-bath for 2 h, and stored in a refrigerator overnight. The product was collected by suction filtration and dried at room temperature/0.25 mmHg for 8 h to give 1.56 g of pure target compound as white crystals, mp 287-288°C (dec), $[\alpha]^{25}_{D}$ -51.8° (c, 1.00, CH_3OH). ^1H NMR (DMSO-d_6) δ 9.37(s, 1 H), 9.22 (s, 1 H), 8.83 (br s, 1 H, D_2O exchangeable), 8.59 (d, J=8.4 Hz, 1H), 8.48 (s, 1 H), 8.03 (m, 2H), 6.11 (br s, 1H, D_2O exchangeable), 5.60 (m, 1 H), 3.22 (m, 1 H), 3.10 (m, 1 H), 2.89 (t, J=7.7 Hz, 2 H), 2.28 (m, 1 H), 2.04 (m, 1 H), 1.60 (quint, J=7.8 Hz, 2 H), 1.33 (hex, J=7.4 Hz, 2 H), 0.89 (t, J=7.4 Hz, 3 H).

Anal. Calcd for $C_{22}H_{22}Cl_2F_3NO \cdot HCl$ (480.80): C, 54.96; H, 4.82; Cl, 22.12; F, 11.86; N, 2.91. Found: C, 54.71; H, 4.88; Cl, 22.00; F, 12.07; N, 2.90.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Tetrahydrofuran-ether-5% NH_4OH (2:2:0.1)	0.70	Homogeneous

Materials

Di-p-toluoyl-D-tartaric acid	Aldrich, Lot No. KG04119PY
dl-Phenanthrenemethanol hydrochloride	Walter Reed Army Institute of Research, Experimental Therapeutics, Lot No. BM08577
Di-p-toluoyl-L-tartaric acid	Aldrich, Lot No. JN11620EG
Dowex 2 x8-200 ion-exchange resin	Aldrich, Lot No. AN05626JG and Bio-Rad, Lot No. 114081C
Methanol	Mallinckrodt, Lot No. 3016KPEP
Ethyl acetate	Fisher Scientific, Lot No. 952084
Ethyl ether	CMS Chempure, Lot No. M102KPNK

4.13 1,5-Dihydro-4H-imidazo[4,5-c]pyridin-4-one (WR 280824)

The synthesis sequence to the title compound is shown in Chart No. 7.

2-Chloropyridine-1-oxide (1): - A 1 L 3-necked flask equipped with a magnetic stirring bar, a thermometer, an addition funnel, and a reflux condenser was charged with 2-chloropyridine (100 g, 0.88 mol) and glacial acetic acid (132 mL). The clear solution was heated to 45°C and 32% peracetic acid (343 mL, 1.63 mol) was added dropwise over 50 min. The mixture was heated at 50°C for 5 h, at 70°C for 17 h, then concentrated (aspirator/ steam bath) to about 160 mL. The residue was diluted with water (150 mL) and concentrated again to about 150 mL. The residue was basified with 40% NaOH solution (70 mL) with ice-cooling and extracted with methylene chloride (3 x 300 mL). The combined extract was washed with brine (1 x 100 mL) and dried over a mixture of magnesium sulfate (50 g) and sodium carbonate (5 g). The solvent was removed under reduced pressure (aspirator, then vacuum pump) to yield 93.3 g (82%) of product as a white solid, mp 66-68°C; lit. mp 66-68°C (20). The product gave a positive Beilstein test.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Methylene chloride-methanol (4:1)	0.71	Homogeneous

Materials

2-Chloropyrine	Aldrich, Lot No. BQ15306CN
Glacial acetic acid	Chempure, Lot No. M002KPRS
Peracetic acid, 32%	Aldrich, Lot No. BQ09909BQ
Sodium hydroxide	Chempure, Lot No. M278KJGH
Methylene chloride	J.T. Baker, Lot No. H40639
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. E25161
Sodium carbonate, anhydrous	Aldrich, Lot No. CZ03112LY

2-Chloro-4-nitropyridine-1-oxide (2): - A 1 L 3-necked flask equipped with a mechanical stirrer, a thermometer, and an addition funnel was charged with concd sulfuric acid (60 mL) which was cooled to 0°C. To the cooled and stirred acid was added 2-chloropyridine-1-oxide (40 g, 308.7 mmol) in portions at such a rate to maintain the temperature at 0-5°C (very exothermic). After the addition was completed, a mixture of fuming nitric acid (Sp. Gr. 1.5, 108 mL) and concd sulfuric acid (60 mL) was added dropwise over a 45 min period while maintaining the temperature at 0-2°C. After the addition was completed, the mixture was heated to 90°C over 1 h and maintained at 90°C for one additional hour. The mixture was cooled to 10°C and poured

onto ice (300 g). The light green solution was treated with sodium carbonate (100 g) and the yellow precipitate was collected by filtration. The solid was air-dried overnight, then dried further at room temperature under vacuum (5 mmHg) for 3 h to give 52.2 g of crude product. The filtrate was treated with powdered sodium hydroxide (110 g) to give a second crop (5.7 g). The combined product (52.2 g + 5.7 g) was dissolved in hot toluene (400 mL). A small water layer was removed from the solution and the organic phase was concentrated (aspirator) to dryness to give 46.6 g of product as light yellow solid.

The reaction was repeated using 53 g of 2-chloropyridine-1-oxide to give 53.4 g of product.

The combined product (45 g + 53 g) was dissolved in boiling toluene (500 mL). The clear solution was stirred at room temperature for 1 h, cooled in an ice-bath for 1.5 h, then refrigerated overnight. The product was collected by filtration and dried at room temperature/0.5 mmHg overnight to give 90.6 g (72%) of pure product as yellow crystals, mp 153-154°C; lit. mp 153-153.5°C (20).

Thin Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Toluene-methanol (9:1)	0.62	Major
	0.22	Trace

Materials

2-Chloropyridine-1-oxide	Ash Stevens Inc., Lot No. CT-7-65
Sulfuric acid	Mallinckrodt, Lot No. 2876KLJX
Fuming nitric acid	Fisher Scientific, Lot No. 865491
Sodium carbonate	Aldrich, Lot No. CZ03112LY
Sodium hydroxide	Chempure, Lot No. M278KJGH
Toluene	J.T. Baker, Lot No. J30661

4-Amino-2-chloropyridine (3): - Iron powder (36.6 g, 0.66 mol) was added to a warm (60°C) solution of compound 2 (32.3 g, 0.18 mol) in glacial acetic acid (320 mL) under a nitrogen atmosphere. The mixture was heated at 70-75°C for 5 min at which time it exothermed. After the exotherm (ca. 115°C) subsided, the thick dark mixture was diluted with additional glacial acetic acid (50 mL) and stirred while maintaining the temperature at 80-85°C for 30 min. The dark mixture was cooled to room temperature and diluted with water (350 mL). The mixture was basified to pH ca. 11-12 by the dropwise addition of 50% (w/w) aqueous sodium hydroxide solution (300 mL) while maintaining the temperature at 40-45°C. The mixture was stirred with ethyl acetate (1 L) for 5

min and filtered through a pad of celite. The filtrate was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 500 mL). The combined organic phase was dried ($MgSO_4$) and filtered through a pad of celite. The filtrate was concentrated (35-40°C/aspirator) to dryness to give crude title compound, 23.1 g, mp 90-92°C.

Following the above procedure, additional crude product, 22.3 g, was obtained from 33.2 g of compound 2.

The combined crude product (45.4 g) was dissolved in hot toluene (350 mL). The hot solution was treated with charcoal (1.5 g) and filtered through a pad of celite. The filtrate was cooled to 70°C and diluted with hexanes (700 mL). The mixture was allowed to cool to room temperature and stirred for 1 h. The off-white solid was collected by filtration and air-dried for 20 h to give pure title compound 3, 44.1 g (91%), mp 91-93°C; lit., mp 91-92°C (21). An analytical sample with the same melting point was obtained from a trial reduction.

Anal. Calcd for $C_5H_5ClN_2$ (128.56): Cl, 27.58. Found: Cl, 27.40.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:1)	0.23	Homogeneous

Materials

Compound 2	Ash Stevens Inc., Lot No. CT-7-84
Glacial acetic acid	Chempure, Lot No. M002KPRS
Iron, powder	Fluka, Lot No. 324666/1 693
Sodium hydroxide solution, 50% (w/w)	J.T. Baker, Lot No. G03043
Ethyl acetate	Fisher Scientific, Lot No. 963378
Magnesium sulfate, anhydrous	J.T. Baker, Lot No. H26142
Toluene	J.T. Baker, Lot No. J30661
Charcoal, Norit A	Aldrich, Lot No. KF02211HF
Celite, analytical	Celite Corp., no Lot No.
Hexanes	J.T. Baker, Lot No. H08776

2-Chloro-4-nitraminopyridine (4): - 4-Amino-2-chloropyridine (22 g, 0.17 mol) was added in small portions over a 15 min period to cold, concentrated sulfuric acid (110 mL) maintained between 0-5°C. The mixture was stirred for 5 min while cooling to -1°C and 90% nitric acid (45 mL) was added dropwise over a 30 min period while maintaining the temperature

at 0-3°C. The solution was allowed to warm to room temperature and stirred for 1 h. The clear yellow solution was poured into a beaker of crushed ice (520 g) cooled in a -30°C dry ice-acetone bath. The pH of the acidic solution was adjusted to ca. 5 by the addition of concentrated ammonium hydroxide solution (350 mL) while maintaining the temperature of the mixture below 15°C. The mixture was warmed to room temperature, stirred for 45 min and the solid was collected by filtration. The solid was combined with similar solid obtained from a second, identical scale reaction and slurried in deionized water (400 mL) for 20 min. The off-white solid was collected by filtration and dried at 25°C/0.1 mmHg for 20 h to give purified title compound 25.6 g (43%), mp 153-154°C; lit., mp 148°C (22), mp 155°C (23). The volume of the filtrate was reduced to ca. 250 mL (30-37°C/aspirator) to give additional purified product, 17.3 g (29%), mp 185°C (dec). Both crops of the purified product were used as such in the next step.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Methylene chloride-methanol-acetic acid-water (88:10:1:1)	0.49	Slight streaking

Materials

Compound 3	Ash Stevens Inc., Lot No. DJD-14-276
Sulfuric acid	Chempure, Lot No. M304KMVY
Nitric acid, 90%	J.T. Baker, Lot No. D50102
Ammonium hydroxide	J.T. Baker, Lot No. H13049

4-Amino-2-chloro-3-nitropyridine (5): - Finely powdered nitramine 4 (25.5 g, 0.147 mol) was added in small portions over a 15 min period to cold, concentrated sulfuric acid maintained between 7-10°C. The mixture was heated to 88-91°C for 30 min and cooled to room temperature. The yellow-orange solution was poured into a beaker of crushed ice (480 g) cooled in a -20°C dry ice-acetone bath. The pH of the strongly acidic solution was adjusted to 2.5 by the addition of concentrated ammonium hydroxide (480 mL) while maintaining the temperature below 15°C. The mixture was allowed to warm to room temperature over 1 h while stirring. The solid was collected by filtration, washed with deionized water (4 x 50 mL) and dried at 35-38°C/0.1 mmHg for 2 h and at room temperature for 17 h. The dried solid (24.6 g) was added to toluene (1.5 L) and the mixture was heated at reflux for 45 min while distilling off a portion of the toluene (250 mL). The resulting yellow-orange solution was filtered through a pad of celite using a jacketed, steam-heated funnel. The filtrate was allowed to cool to room temperature over 90 min.

The light yellow-orange solid was collected by filtration, washed with hexanes (2 x 50 mL) and air-dried for 20 h to give purified compound 5, 12.3 g, mp 205-207°C.

By the above procedure, additional purified product 5 (6 g, mp 207-209°C) was obtained from the second crop of crude compound 4 (17.2 g, mp 185°C, dec).

The combined purified product (18.1 g) was dissolved in hot ethanol (500 mL). The hot solution was treated with charcoal (1 g) and filtered through a pad of celite using a jacketed steam-heated funnel. The volume of the filtrate was reduced to ca. 250 mL (30-35°C/aspirator) and the mixture was heated to obtain a solution. The solution was allowed to cool to room temperature over 2.5 h while stirring. The yellow solid was collected by filtration, washed with hexanes (3 x 50 mL), and air-dried for 20 h to give pure product, 13.3 g (31%), mp 212-214°C; lit., mp 209-210°C (14). Concentration of the filtrate gave a second crop, 3.5 g (8%), mp 211-213°C.

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:1)	0.27	Homogeneous

Materials

Compound 4	Ash Stevens Inc., Lot No. DJD-14-279
Sulfuric acid	Chempure, Lot No. M304KMVY
Ammonium hydroxide	J.T. Baker, Lot No. H13049
Toluene	J.T. Baker, Lot No. J30661
Celite, tech	Celite Corp., Lot No. C5453AP301016
Ethanol	Baxter Diagnostics, Lot No. 6038
Charcoal, Norit A	Aldrich, Lot No. KF02211KF
Hexanes	J.T. Baker, Lot No. H08776
Water, deionized	Ash Stevens Inc., no Lot No.

2-Chloro-3,4-diaminopyridine (7): - Wet Raney Nickel (6.6 g) was added to a suspension of compound 5 (6.25 g, 0.036 mol) in ethanol (250 mL) and the mixture was hydrogenated at 50 psi in a Parr hydrogenation apparatus for 1 h. Analysis by TLC (Analtech, EtOAc-hexanes, 1:1) showed the absence of starting material. The catalyst was removed by filtration through a pad of celite and washed with ethanol (2 x 25 mL). The combined light yellow filtrate was concentrated to dryness (40-45°C/aspirator) to give a solid, 5.1 g. The solid was extracted with hot acetone (3 x 150 mL). The combined extract was cooled to room temperature and passed through a column of silica gel (30 g, 15.5 x 3 cm). The

column was washed with additional acetone (750 mL). The product-containing fractions were combined and concentrated to dryness (30-35°C/aspirator) to give purified product 7, 3.9 g. The purified product (3.9 g) was stirred with refluxing toluene (50 mL) and the near-solution was cooled to ca. 50°C and diluted with hexanes (100 mL). The mixture was stirred for 30 min and filtered. The off-white solid was washed with hexanes (2 x 25 mL) and air-dried for 20 h to give pure compound 7, 3.5 g (68%), mp 159-161°C; lit., mp 155°C (22).

Thin-Layer Chromatography EM Science Kieselgel 60 F_{254}

Eluent	Rf	Comment
Ethyl acetate-hexanes (1:1)	0.12	Homogeneous

Materials

Compound 5	Ash Stevens Inc., Lot No. DJD-14-283
Ethanol	Baxter Diagnostics, Lot No. 6038
Raney Nickel	Aldrich, Lot No. AM5125ML
Hydrogen	Airco, Grade 5, no Lot No.
Celite, tech	Celite Corp., Lot No. C5453AP301016
Acetone	J.T. Baker, Lot No. K05673
Silica gel	J.T. Baker, Lot No. 439348
Toluene	J.T. Baker, Lot No. J30661
Hexanes	J.T. Baker, Lot No. H08776

1,5-Dihydro-4H-imidazo[4,5-c]pyridin-4-one (WR 280824) (8): - A solution of compound 7 (3.5 g, 0.024 mol) in formic acid (7 mL) was heated at reflux under a nitrogen atmosphere and the reaction was monitored by TLC (Analtech, methylene chloride-methanol-acetic acid-water, 88:10:1:1). Analysis at 2 h showed that no further change was taking place. The excess formic acid was removed under reduced pressure (steam bath/aspirator, then 50-55°C/0.1 mmHg). The residual solid was dissolved in hot deionized water (35 mL) and the solution was cooled to 10-15°C. The solution was adjusted to pH 6-7 by the portionwise addition (foaming) of potassium bicarbonate (4.25 g, 0.042 mol). The mixture was allowed to warm to room temperature and stirred for 30 min. The off-white solid was collected by filtration and the damp solid was dissolved in hot water (50 mL). The hot solution was filtered (gravity) and the light yellow filtrate was stored undisturbed at room temperature for 41 h. The beige solid was collected and air-dried for 90 min to give purified product 8, 1.71 g. Analysis by TLC showed it to be 80-85% pure with one

major non-polar impurity. This product was recrystallized twice from deionized water (35 mL and 25 mL) and dried at 100°C/0.1 mmHg for 90 min to give pure title compound 8, 0.7 g (21%), mp >325°C; lit., mp >360°C (15).

Anal. Calcd for $C_6H_5N_3O$ (135.13): C, 53.33; H, 3.73; N, 31.09. Found: C, 53.10; H, 3.74; N, 30.88.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Methylene chloride-methanol-acetic acid-water (88:10:1:1)	0.18	Homogeneous

Materials

Compound 7	Ash Stevens Inc., Lot No. DJD-14-288
Formic acid, 98%	Fluka, Lot No. 44877/1 496
Potassium bicarbonate	Fluka, Lot No. 331051/1 196
Water, deionized	Ash Stevens Inc., no Lot No.

4.14 8-[(3-Carboxy-1-methylpropyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (WR 280829)

A mixture of 8-amino-5-(1-hexyloxy)-6-methoxy-4-methylquinoline (6 g, 20.8 mmol), levulinic acid (14.5 g, 124.8 mmol), powdered 3A molecular sieves (7.5 g), and methanol (45 mL) was stirred at room temperature for 1.5 h under a nitrogen blanket. The mixture was chilled in an ice-bath, and a solution of sodium cyanoborohydride (1.3 g, 20.8 mmol) in methanol (12 mL) was added dropwise to the stirred mixture. The mixture was stirred in the ice-bath for an additional 10 min and then at room temperature for 3 h. The mixture was filtered through a celite pad and the celite pad was washed with methanol (20 mL). The combined filtrate was concentrated (aspirator) to about 15 mL and was partitioned between methylene chloride (100 mL) and water (100 mL). The layers were separated, and the water layer was extracted with methylene chloride (50 mL). The combined organic layer was washed with water (100 mL), brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (aspirator and then oil pump) to give a thick, dark brown oil (10.3 g). The oil was chromatographed over silica gel (300 g, 5 cm x 35 cm), eluting with a mixture of ethyl acetate and hexanes (1:1). Fractions containing product were combined and evaporated (aspirator and then oil pump) to give a dark brown oil (5.2 g). The oil solidified when triturated with hexanes (50 mL) to give 4.4 g of crude product as light brown solid. The solid was dissolved in ether (50 mL). The solution was treated with charcoal (4 g) and filtered through a celite pad. The yellow filtrate was filtered again through regular filter paper and

evaporated (aspirator). The residue was dissolved in ether (20 mL) and filtered. The clear filtrate was diluted slowly with petroleum ether (40 mL) and refrigerated for 3 h. The solid was collected by suction filtration and dried at room temperature/0.2 mmHg for 17 h to give 3.4 g (42%) of pure target compound as bright yellow crystals, mp 65.5-67.5°C. ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1 H, D_2O exchangeable), 8.35 (d, J=4.3 Hz, 1 H, QH-2), 7.17 (d, J=4.2 Hz, 1 H, QH-3), 6.63 (s, 1 H, QH-7), 6.11 (br d, J=8.4 Hz, 1 H, D_2O exchangeable), 3.90 (s, 3 H, OCH_3), 3.80 (t, J=6.7 Hz, 2 H, OCH_2), 3.70 (m, 1 H, NCH), 2.77 (s, 3 H, QCH_3), 2.34 (t, J=7.2 Hz, 2 H, CH_2CO_2), 1.93 (m, 1 H, NCH$\underline{CH}$), 1.80-1.60 (m, 3 H, NCH$\underline{CH}$, $OCH_2\underline{CH_2}$), 1.50-1.35 (m, 2 H,)$OCH_2CH_2\underline{CH_2}$), 1.35-1.25 (m, 4 H, $(CH_2)_2$), 1.23 (d, J=6.4 Hz, 3 H, $CH\underline{CH_3}$), 0.88 (t, J=6.9 Hz, 3 H, $CH_2\underline{CH_3}$).

Anal. Calcd for $C_{22}H_{32}N_2O_4$ (388.49): C, 68.01; H, 8.30; N, 7.21. Found: C, 67.89; H, 8.26; N, 7.15.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Tetrahydrofuran-methanol-5% NH_4OH (10:1:1)	0.25	Homogeneous
Toluene-methanol-formic acid (10:1:0.1)	0.29	Homogeneous

Materials

8-Amino-5-(1-hexyloxy)-6-methoxy-4-methylquinoline	Ash Stevens Inc., Lot No. KB-02-59
Levulinic acid	Aldrich, Lot No. LN23005LN
Methanol	Mallinckrodt, Lot No. 3016KPEP
3A Molecular sieves	Aldrich, Lot No. KP03219KP
Sodium cyanoborohydride	Aldrich, Lot No. DQ18128LN
Methylene chloride	J.T. Baker, Lot No. J51613
Celite	Celite Corp., Lot No. 307
Magnesium sulfate	J.T. Baker, Lot No. E25161
Silica gel	EM Science, Lot No. TA770634-516
Ethyl acetate	Fisher Scientific, Lot No. 952084
Hexanes	J.T. Baker, Lot No. J51694
Charcoal	Fluka, Lot No. 301730-1-891
Ethyl ether	CMS Chempure, Lot No. M102KPNK
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. K03739

4.15 2-Chloro-5-(trifluoromethyl)benzenesulfonyl chloride (WR 280846)

A 200 mL 3-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel was charged with concd HCl (51 mL) and acetic acid (15 mL). With ice-cooling, 3-amino-4-chlorobenzotrifluoride (30 g, 153.4 mmol) was added in one portion to the solution. A white solid was deposited immediately. The mixture was cooled to below -10°C (dry ice-acetone) and a solution of sodium nitrite (11.7 g, 169.6 mmol) in water (17 mL) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed -5°C. After the addition was completed, the mixture was stirred at -10°C to -5°C for 45 min. A separate 500 mL 3-necked flask equipped with a mechanical stirrer and a gas inlet tube was charged with acetic acid (153 mL). At room temperature, sulfur dioxide was bubbled into the solvent until saturation (ca. 15 min), and cuprous chloride (3.8 g) was added to the solution. The introduction of sulfur dioxide was continued until the yellow-green solution became blue-green (ca. 30 min). The gas inlet tube was replaced with a thermometer. The mixture was then cooled to 10°C and the diazonium salt mixture was added in portions. Considerable foaming occurred after each addition. The temperature of the reaction mixture was maintained at 7-8°C. After the addition of the diazonium salt mixture was completed, the reaction mixture (dark green color) was poured into ice-water (1:1, 400 mL) and the mixture was extracted with ether (2 x 400 mL, 1 x 200 mL). The combined ether extract was washed with ice water (5 x 400 mL), ice cold saturated aq. sodium bicarbonate (2 x 400 mL), ice cold brine (1 x 400 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure (aspirator, then oil pump) to give crude product (36.2 g) as a light brown oil which solidified in the freezer.

In the same manner, another 30 g of aniline was processed to yield 36.1 g of crude product.

The combined crude product (72.3 g) was chromatographed (SiO_2, 400 g) eluting with a mixture of petroleum ether-ethyl ether (9:1). Fractions containing the product were combined, treated with charcoal (6 g), and filtered through a celite pad. The solvent was removed under reduced pressure and the residual oil was distilled to give 56.7 g (66%) of pure product as a yellow clear oil, bp 85-89°C/0.75 mmHg. The oil solidified in the freezer but the solid melted at room temperature. ^1H NMR ($CDCl_3$) δ 8.40 (d, J=1.8 Hz, 1 H), 7.92 (dd, J=2.1, 8.5 Hz, 1 H), 7.82 (d, J=8.7 Hz, 1 H).

Anal. Calcd for $C_7H_3Cl_2F_3SO_2$ (279.07): C, 30.13; H, 1.08; Cl, 25.41; F, 20.42; S, 11.49. Found: C, 30.02; H, 1.14; Cl, 25.52; F, 20.38; S, 11.42.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Toluene-petroleum ether (1:9)	0.35	Slight streaking
Ether-petroleum ether (1:9)	0.62	Slight streaking

Materials

3-Amino-4-chlorobenzotrifluoride	Aldrich, Lot No. DQ00527TN
Sodium nitrite	Aldrich, Lot No. 07324KG
Hydrochloric acid	Chempure, Lot No. M152KPCX
Acetic acid	CMS Chempure, Lot No. M002KPRS
Sulfur dioxide	Liquid Carbonic Co., no Lot No
Cuprous chloride	Fluka, Lot No. 350172-1-1095
Ethyl ether	Fisher Scientific, Lot No. 967049-15
Sodium bicarbonate	Aldrich, Lot No. BG00729LF
Magnesium sulfate	J.T. Baker, Lot No. E25161
Silica gel	EM Science, Lot No. TA770634-516
Petroleum ether (bp 38.1-54.9°C)	Fisher Scientific, Lot No. 963355

4.16 8-[(4-Amino-1-methylbutyl)amino]-5,6-dihydroxy-4-methylquinoline hydrobromide, hydrate (WR 280870)

8-[(4-Amino-1-methylbutyl)amino]-6-benzyloxy-5-(1-hexyloxy)-4-methylquinoline dihydrobromide: - A solution of 8-[(4-amino-1-methylbutyl)amino]-6-benzyloxy-5-(1-hexyloxy)-4-methylquinoline dihydrochloride (8 g, 15.3 mmol) in methanol (40 mL) was passed through a Dowex 2-X8 base-form resin column (ca. 150 mL, 180 meq) and the column was washed with methanol. As the product eluted from the column, 47% aq. HBr solution (7.9 g, 45.9 mmol) was added dropwise simultaneously to the eluate. The solution was concentrated to near dryness (aspirator) and the residue was co-evaporated (aspirator and pump) with toluene (20 mL) to give a reddish orange color wet solid (19 g). The solid was dissolved in hot ethanol (90 mL) and the solution was filtered. The filtrate was stirred and diluted with isopropanol (90 mL). The mixture was stirred at room temperature for 30 min and in an ice-bath for 1 h. The mixture was filtered to give 8.5 g (91%) of pure product as reddish orange crystals, mp 190-192°C (dec). ^{1}H NMR (DMSO-d_6) δ 8.62 (d, J=4.3 Hz, 1 H), 7.87 (br s, 1 H, D_2O exchangeable), 7.55-7.53 (m, 2 H), 7.48-7.30 (m, 5 H), 5.34 (s, 2 H), 3.98 (m, 2 H), 2.92 (s, 3 H), 2.84 (s, 2 H), 1.75-1.69 (m, 6 H), 1.45-1.90 (m, 10 H), 0.84 (br t, J=6.9 Hz, 3 H).

Anal. Calcd for $C_{28}H_{39}N_3O_2 \cdot 2HBr$ (611.48): C, 55.00; H, 6.76; Br, 26.14; N, 6.87. Found: C, 54.78; H, 6.78; Br, 26.11; N, 6.80.

Thin-Layer Chromatography Analtech HPTLC-RPSF

Eluent	Rf	Comment
Methanol-0.2 M NaH_2PO_4 (20:1)	0.24	Homogeneous

Materials

Quinoline dihydrochloride	Ash Stevens Inc., Lot No. DJD-14-244
Methanol	Mallinckrodt, Lot No. 3016KPEP
Hydrobromic acid, 47%	J.T. Baker, Lot No. C15335
Dowex 2-X8	Aldrich, Lot No. AN05626JG
Toluene	J.T. Baker, Lot No. J30661
Isopropanol	Chempure, Lot No. M158KPHA

8-[(4-Amino-1-methylbutyl)amino]-5,6-dihydroxy-4-methylquinoline hydrobromide (WR 280870): - All solvents used for the following process were freed of gaseous oxygen. At room temperature, 8-[(4-amino-1-methylbutyl)amino]-6-benzyloxy-5-(1-hexyloxy)-4-methylquinoline dihydrobromide (8 g, 13.08 mmol) was hydrogenated (50 psi) for 1 h over palladium black catalyst (800 mg) in methanol (80 mL). The reaction mixture was filtered under nitrogen and the filtrate was evaporated under reduced pressure (aspirator). The residue was heated in 47% HBr (5 mL) at reflux for 1 h. After cooling, the reaction mixture was evaporated (aspirator), and the residue was dissolved in a mixture of toluene (20 mL) and methanol (20 mL) and concentrated (aspirator) to a yellowish brown solid. The solid was dissolved in a hot mixture of methanol (10 mL) and ethanol (60 mL) containing 47% HBr (0.05 mL). After cooling, the solution was diluted slowly with petroleum ether (60 mL) with stirring. The mixture was stored in a refrigerator overnight, then filtered to yield 3.91 g of the product as a beige solid. The solid was dissolved in a warm mixture of methanol (5 mL) and ethanol (30 mL) containing 47% HBr (0.05 mL) and the solution was filtered under nitrogen. The clear filtrate was slowly diluted with petroleum ether (20 mL) with stirring. The mixture was stirred in an ice-bath for 1.5 h and stored in a refrigerator overnight. The cold mixture was warmed to ambient temperature and filtered under nitrogen. The solid was dried at 60°C/0.5 mmHg for 3 h to give 2.57 g (38%) of pure target compound as yellow crystals, mp 209-211°C (dec). ^1H NMR (DMSO-d_6) δ 9.10 (br s, 5 H, D_2O exchangeable), 7.66 (s, 1 H), 7.36 (d, J=4.7, 1 H), 3.75 (m, 1 H), 2.94 (s, 3 H), 2.80 (m, 2 H), 1.90-1.60 (m, 4 H), 1.28 (d, J=6.5 Hz, 3 H).

Anal. Calcd for $C_{15}H_{21}N_3O_2 \cdot 2.9HBr \cdot 0.5H_2O$ (519.04): C, 34.71; H, 4.84; Br, 44.65; N, 8.10. Found: C, 34.64; H, 4.72; Br, 44.75; N, 7.88.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Methanol-toluene-5% NH_4OH (7:3:1)	0.23	Major product
	0.74	Minor impurity

Materials

Quinoline dihydrobromide	Ash Stevens Inc., Lot No. CT-7-165
Palladium black	Aldrich, Lot No. KN15710KN
Methanol	Mallinckrodt, Lot No. 3016KPEP
Hydrobromic acid, 47%	J.T. Baker, Lot No. C-15335
Ethanol	CMS Chempure, Lot No. M256KPPR
Petroleum ether (bp 38.1-54.9°C)	Fisher Scientific, Lot No. 963355

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